PAIN, PAIN MANAGEMENT, AND QUALITY OF LIFE IN EHLERS-DANLOS RELATED DISORDERS

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ABSTRACT

Ehlers-Danlos syndrome (EDS) is a group of inherited connective tissue disorders that result in joint hypermobility, skin fragility, and chronic pain. Undiagnosed connective tissue disorder (UCTD) describes individuals who present with symptoms consistent with a connective tissue disorder, but do not have a confirmed clinical or genetic diagnosis. A quantitative study was conducted to investigate the relationship between pain and quality of life (QOL) in individuals with EDS or UCTD. The types of pain management techniques used and their reported effectiveness were also investigated. Adults (n = 23) and children (n = 7) with EDS or UCTD completed questionnaires on pain (PQAS© for adults and PedsQL™ Pediatric Pain Questionnaire ™ for children), quality of life (PedsQL™ Generic Core Scale) and pain management. The results demonstrated that chronic pain is common, with variability in the type and frequency of pain experienced. Increased pain is significantly related to decreased quality of life in the adult sample ($p < 0.01$). The majority (85.7%) of the participants in this sample used pain management techniques and reported a wide variety of management types. In conclusion, the findings in the present study suggest that pain is common and may impact the QOL of individuals with EDS and UCTD. The public health impact of this study is to increase awareness of EDS and UCTD and the difficulties in treating and managing these conditions. Future studies are warranted to determine which pain management techniques are most effective in improving QOL in EDS and UCTD.

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PREFACE

I would first and foremost like to thank Juliann McConnell for giving me the opportunity to work on this project. I am very grateful for her guidance, knowledge, and support throughout this process, without which I would not have been able to successfully complete this project. I would also like to acknowledge my two other committee members, Dr. John Shaffer and Dr. Beth Nolan for being willing to serve on my committee and their constant support and helpful suggestions throughout this project. In addition, I would like to thank Dr. Suneeta Madan-Khetarpal for serving as principal investigator on this project and providing her expertise.

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1.0 INTRODUCTION

Connective tissue disorders (CTD) are a group of inherited conditions caused by mutations in genes encoding for elastin and collagen, which are two proteins in the body important for connective tissue development and structure. There are many different types of connective tissue disorders that involve many different genes and have widely varying manifestations.

Ehlers-Danlos syndrome (EDS) is the most common CTD. There are six different types of EDS that have variable clinical symptoms. These symptoms can include issues of the skin, joints, blood vessels, and organs. Undiagnosed connective tissue disorder (UCTD) are individuals who present with symptoms consistent with a connective tissue disorder, but do not have a confirmed clinical or genetic diagnosis. There is a lot of overlap in CTD symptoms, so these individuals have not been classified in a particular type of CTD. In many cases, those with UCTD have a suspected diagnosis of EDS, but have not been able to confirm the diagnosis with clinical criteria or genetic testing. Many individuals with EDS and UCTD present with mild to severe pain. The pain in EDS and UCTD is primarily characterized as musculoskeletal pain.

This main goal of this study was to survey a population of individuals with these conditions to determine if there is a relationship between pain and quality of life (QOL). This study also aims to determine if any other factor was associated with pain or quality of life in this sample. This study hopes to also determine which pain management techniques these populations use and which techniques have been most successful. The desired outcome is to

learn more information about the amount of pain experienced by these individuals, the effect the pain has on their quality of life, and the most effective pain management techniques.

1.1 AIMS

Aim 1: To characterize the types of pain experienced by individuals with EDS and UCTD.

Aim 2: To determine the pain management techniques that EDS and UCTD patients use to relieve or reduce their pain, and determine which techniques they report to be the most effective.

Aim 3: To assess the relationship between pain and quality of life in individuals with EDS and UCTD. In the adult population, it is hypothesized that increased pain will be correlated with decreased quality of life in these participants.

Aim 4: To investigate other factors that may relate to pain or quality of life in this sample, such as age, sex, or the use of pain management techniques. It is hypothesized that age will be related to increased pain and decreased quality of life.

1.2 BACKGROUND AND SIGNIFICANCE

1.2.1 Connective Tissue in Humans and Connective Tissue Disorders

In the human body, connective tissue acts as a structural support framework needed for growth, development, and protection of vital organs. Types of connective tissue in the body are skin, tendons, ligaments, cartilage, and bone [1, 2]. Connective tissue interacts in a complex system

called the extracellular matrix (ECM), which consists of structural proteins (collagen and elastin), specialized proteins (fibrillin, fibronectin, and laminin), and proteoglycans [1, 2]. Mutations of genes that encode for a protein involved in the ECM can result in a connective tissue disorder (CTD).

1.2.2 Ehlers-Danlos Syndrome and Undiagnosed Connective Tissue Disorder

Ehlers-Danlos Syndrome (EDS) is a group of heterogeneous inherited connective tissue disorders that primarily affects the skin, ligaments, joints, and blood vessels [2, 3]. EDS is one of the oldest known disorders of bruising and bleeding and was first described by Hippocrates in 400 BC [4]. A Danish dermatologist named Edvard Ehlers first recognized EDS as a distinct disorder in 1901 and a French dermatologist named Henri-Alexandre Danlos suggested that the skin extensibility and fragility were also features of the same condition in 1908 [4]. An English physician named Frederick Parkes-Weber suggested the disorder be named 'Ehlers-Danlos syndrome" in 1936 [4].

Table 1 Revised Classification of EDS Types
Joint hypermobility, (JHM) [5]

Type	Inheritance	Gene	Clinical Manifestations
Classical (EDS I and II)	AD	COL5A1 COL5A2	Skin laxity, atrophic scars, JHM, hypotonia, hernias, velvety skin
Hypermobility (EDS III)	AD	TNX-B	Skin laxity, JHM, frequent recurring joint dislocations, chronic joint pain
Vascular (EDS IV)	AD	COL3A1	Arterial/intestinal rupture, easy bruising, thin skin, varicose veins, JHM
Kyphoscoliosis (EDS VI)	AR	LH-1	Joint laxity, muscle hypotonia, kyphoscoliosis, sclera fragility
Arthrochalasis (EDS VIIA&B)	AD	COL1A1 COL1A2	JHM, congenital hip dislocation, muscle hypotonia, kyphoscoliosis
Dermatosparaxis (EDS VIIC)	AR	ADAMTS-2	Sagging redundant skin, excessive bruising, severe skin fragility, soft/doughy skin

The current literature classifies EDS as a rare disease with a frequency between 1 in 10,000 and 1 in 25,000 people, however EDS is thought to be a highly under diagnosed condition [3]. There are many types of EDS with different clinical features, inheritance patterns, and genetics, which are reviewed in Table 1 above. The most common forms of EDS are EDS hypermobility type (EDS-HT), classic EDS, and vascular EDS [3]. The classic symptoms include hyperextensible skin, hypermobile joints, dystrophic scarring, fragile connective tissue, and easy bruising [2, 3, 5]. Skin is often velvety, thin, and easily splits with little or no trauma [2, 3]. Individuals with EDS can also have difficulty and delay in healing, which eventually lead to atrophic scars [2, 3]. EDS can also lead to frequent joint dislocations, especially in the hip, patella, shoulders, and hands [2, 3]. Due to the wide range of manifestations of this disorder, many aspects of an individual's life can be affected including physical and psychologically [2, 3]. Additional features include fatigue, anxiety, and depression which have been thought to be a result of the chronic and debilitating pain [6, 7].

There is some genetic testing for EDS that can be performed, however this testing does not identify a genetic cause for all individuals with a clinical EDS diagnosis. Previous literature has indicated that of individuals that met all major criteria for Villefranche criteria for classic EDS, more than 90% had a COL5A1 or COL5A2 defect [8, 9]. Genetic testing for EDS-HT involves looking for mutations in the TNX gene, however no more than 10% of individuals with a clinical EDS-HT diagnosis have a mutation in this gene [10, 11]. This suggests that there are other genes or genetic loci involved in EDS.

The variability in EDS results in misdiagnosis, delay to diagnosis, and never being diagnosed. The variability in the clinical picture of this condition contributes to this problem [12]. The lack of a correct diagnosis has been shown to affect the functionality of these

individuals due to financial expenses, unnecessary medical testing, use of incorrect treatments, delay in appropriate management, and the progression of disease [6, 12]. Due to the difficulties in diagnoses, many individuals with EDS are not diagnosed until after childhood [13]. These complications demonstrate the need for more studies that include individuals with an UCTD and suspected EDS.

1.2.3 Pain in EDS and UCTD

Chronic pain is a common feature, but highly variable among individuals with EDS [12, 14, 15]. Some studies have reported as much as 90% of individuals with classic EDS or EDS-HT reporting at least moderate pain with the duration of pain being at least one year [15, 16]. In Castori et al., individuals with EDS and EDS-HT from Italy reported increased chronic musculoskeletal pain and fatigue, however pain was more likely in individuals with EDS-HT and was associated with hypermobility and dislocations [6]. The locations most frequently affected are the shoulders, hands, and knees [15]. Many previous studies have been done that have described the many types of pain experienced in EDS-HT including: dislocations, arthralgias, back pain, myalgias/myofascial pain, compression neuropathy, peripheral neuropathy, headache disorders, and abdominal pain [14, 15, 17, 18]. Musculoskeletal pain is a very common feature in EDS-HT and is associated with regular analgesic use, joint hypermobility, dislocations, corrective surgery, and related to functional impairment [14, 15]. Pain is recognized as a major criteria of JHS and in the minor criteria of the Villefranche criteria revised nosology for EDS-HT [5, 19].

There is limited information about the origin of pain in EDS. It is thought to be caused by joint damage due to frequent dislocations or soft tissue injury, which is secondary to the

disease manifestations [15]. Interestingly, pain in EDS is not thought to be neuropathic in origin, however more than 30% of individuals with EDS report neuropathic pain [16, 18] . Little information is known about the origin of the pain in EDS. Joint hypermobility syndrome (JHS) is sometimes used interchangeably with EDS hypermobility type due to the chronic nature of their joint laxity, however these are now thought to be separate conditions that have similar features [19].

Arthralgias, back pain, and myalgias occur in 30% of children with JHS/EDS-HT, while more than 80% of adults over forty experience these manifestations [17]. Another issue that faces many individuals with EDS-HT is that they may not always meet the diagnostic criteria and there are different criteria to follow. The Beighton score which tends to fall below 4/9 at a mean age of 33 years in JHS/EDS-HT even individuals with many and severe disease manifestations [17]. Due to these findings, it is thought that pediatric and younger patients that generally display greater joint mobility and less pain symptoms may have a greater chance of meeting the Villefranche criteria [17, 20]. The Beighton criteria seem to better fit adult patients who experience greater pain and musculoskeletal manifestations, but have lost some of the flexibility and hypermobility they once experienced in their childhood [17, 20]. It has been suggested that there should be a shift in a diagnostic criteria that would incorporate the age, sex, and clinical history of patient [20].

Previous studies have also shown the importance of differentiating between nociceptive and neuropathic pain to develop more efficient treatments for EDS patients [16]. Previous literature has described three separate stages of EDS in the natural history of the disease: hypermobility, pain, and stiffness, again suggesting that the pain is secondary to the already existing musculoskeletal problems associated with EDS [6, 16, 21]. The theory developed from

these studies is that treatments need to target patients during the first phase in order to prevent the pain and stiffness phases.

Some studies have shown an association between hypermobility and dislocations, however they have not investigate the actual origin of pain in EDS [18, 21]. However, some studies have targeted the mechanisms behind the pain associated with EDS. One study conducted by Vooermans et al. showed that axonal polyneuropathy occurs in various types of EDS. In the participants, 60% had reduced sensation, 40% had some reduced distal muscle force, and 25% had reduced reflexes [22]. Nerve conduction studies were abnormal in 38% and criteria for axonal polyneuropathy was met in 13% of patients [22].

1.2.4 Pain and Quality of Life

Pain is a factor that can substantially alter an individual's quality of life [23, 24]. Quality of life (QOL) is a term generally accepted in the medical field, which defines a person's overall wellbeing. QOL is often used for populations, which experience chronic or disabling conditions, such as arthritis.

The potential effect that EDS may have on a patient's quality of life is rarely investigated by physicians or in the current literature [25]. EDS symptoms often go unrecognized for years and patients are affected not only by being symptomatic, but also by being dismissed by practitioners, relatives, and friends [12]. This suggests that EDS and the associated chronic pain, fatigue, and other neurological features likely representing major risk factors for disability [26, 27].

In a 2010 study by Voermans et al. of 273 individuals with EDS, pain was related to functional impairment in daily life [14]. In this study, pain severity was related to disability, which has been reported in prior populations [28]

1.2.5 Pain Management and Treatment in EDS and UCTD

The treatment and management for EDS-HT can be frustrating for both patients and healthcare providers due to the lack of long-term relief or effective treatments. Unfortunately, JHM or EDS-HT are sometimes still considered to be a benign syndrome that may only be important when planning surgeries due to frequent complications [29].

Some recent studies have focused on identifying possible treatment options for individuals with EDS and to eventually create guidelines for management. Some examples of prevention strategies for pain in EDS are light aerobic fitness, weight control, stretching, strength exercises, and avoiding strenuous exercise [29]. Some examples of first-line treatments include: rest, stretching, joint manipulation, heat therapy, acupuncture, stretching, and physical therapy [29]. Suggested treatments for more severe pain are pain medication (non-steroidal anti-inflammatory drugs, corticosteroids, opioids, muscle relaxants), surgery, join injections, and anti-depressants [29]. In a 2010 study by Voermans et al., 89% of 273 individuals with a type of EDS used some type of pain medication, which was associated with chronic pain [14].

The treatments for EDS vary widely. However, accumulated evidence suggests the importance of increasing awareness of CTDs, especially EDS-HT, in order to identify preventive, therapeutic, and rehabilitative strategies to preserve function and quality of life in

these patients [29]. As was previously mentioned, the current thought is that an individual's sex, age, and clinical manifestations should be taken into account when treating EDS [12, 17].

1.2.6 Significance

This study aims to examine the relationship between pain and quality of life in individuals with EDS and UCTD. This study also will investigate if sex, age, or the use of pain management techniques is associated with quality of life. There have been some previous studies that have focused on the EDS population and quality of life. However, these studies did not include individuals with UCTD or a suspected EDS diagnosis. Also, there have been limited studies that have investigated the relationship between pain management use and quality of life, which could allow for a better understanding of the effectiveness of pain management in this population. Also, there is limited information in the previous literature about which pain management methods this population is actually using and which they believe to be most effective. This could help to develop better pain management programs that use one or multiple techniques that best relieve pain in for individuals with EDS. It is important that this population receive better medical treatment as many of them experience debilitating pain on a regular basis that can affect their daily lives.

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2.0 MATERIALS AND METHODS

2.1 DATA COLLECTION

2.1.1 Patient Population

The patient population consisted of male and female patients that were evaluated by one of the physicians in the Department of Medical Genetics at the Children's Hospital of Pittsburgh. Inclusion criteria were that participants had to be between the ages of eight and 80 and had to be diagnosed with EDS or EDS-like symptoms. Exclusion criteria were any patients under the age of eight or over the age of 80 and anyone without one of these two diagnoses.

2.1.2 Patient Recruitment

Patients were recruited through the Department of Medical Genetics at the Children's Hospital of Pittsburgh. Any patient that had been evaluated by one of the physicians, given a diagnosis of EDS or undiagnosed connective tissue disorder, and between the ages of eight and 80 was eligible for this study. Patients were evaluated at the Department of Medical Genetics in February 2014 or earlier. All recruitment was compliant with IRB protocol number PRO13080515 (Appendix A). A genetic counseling intern and a genetic counselor recruited

patients by identifying patients that met criteria to participate and sending the survey materials to those individuals (Appendix B).

2.1.3 Informed Consent

Informed consent involved describing the aims of the research project, as well as the requirements to participate, the rights of the participants, and the risks and benefits associated with the study (Appendix C). Since this study involved minimal risk, the consent form was sent to the participants with the survey materials for them to review at their convenience. After reading the consent form, the participants provided a signature, printed name, and data on the last page of the consent form. In participants under the age of 18, both the parent and child signed the consent form. The consent form was sent back with the survey materials. No surveys were obtained or included in the study without written consent by participants or their parents.

2.1.4 Sample

The total number of eligible participants was 125, which were all recruited through the Department of Medical Genetics at the Children's Hospital of Pittsburgh. Of the 125 surveys sent, 69 (55.2%) were sent to individuals over 18 and 56 (44.8%) were sent to those under the age of 18. Of the adults, 55 (79.7%) surveys were sent to females and 14 (20.3%) were sent to males. Of the children, 29 (51.8%) were sent to females and 27 (48.2%) were sent to males.

Of 125 eligible participants, 30 (24%) returned the surveys by mail. Of the 69 surveys sent to adults, 23 (33.3%) were returned. Of the 55 surveys sent to children, 7 (12.5%) were returned. Of the 55 female adults, 22 (40%) were returned. Of the 14 male adults, one (7%) was

returned. Of the 29 female children, 3 (10%) were returned. Of the 27 male children, 4 (14.8%) were returned.

2.1.5 Tools

The PedsQL ™ Pediatric Pain Questionnaire ™ (PPQ ™), Pediatric Quality of Life Inventory (PedsQL™), and Pain Quality Assessment Scale© (PQAS©) appeared to be the optimal instruments for the current to collect the desired data. The last questionnaire was created to determine which specific pain management techniques were being used and which were the most effective. All of the surveys are included in Appendix D.

Pediatric Pain Questionnaire ™

Pain for the participants under age 18 was assessed through the Pediatric Pain Questionnaire ™ (PPQ ™)[30]. The PPQ ™ is a patient self-reported and age-specific questionnaire. The PPQ ™ assesses the intensity and locations of pain. It also examines more subjective characteristics of a patient's pain and allows them to describe with an open-ended question. The PPQ ™ includes a 100 mm horizontal line or a visual analog scale. The scale is a range that begins with a smiling cartoon face with "no hurt at all" or by "no pain, not hurting, no discomfort". The scale ends with a sad cartoon face and "hurting a whole lot" or by "severe pain, hurting a whole lot, very uncomfortable". The survey also included an outline of a human body and asks the subject to place an "X" on the drawing in every area that they were currently experiencing pain and to rank those areas, with one being the most painful. PPQ ™ has been shown in previous literature to be a reliable and valid tool to measure pediatric self-reported chronic pain intensity [30]

Pain Quality Assessment Scale©

Pain in adults was assessed through the Pain Quality Assessment Scale© (PQAS©), which is a valid and reliable tool to assess pain quality [31, 32]. The PQAS© asks patients to rate their average pain intensity over the past week on a 0-10 numerical rating scale, with 0 = "No Pain" and 10 = "The most intense pain sensation".

Pain quality was assessed using a composite of the 20 items. Each item assesses a different quality of pain. Of the 20 total items, 15 items can be used to three subscores for paroxysmal, surface, and deep pain. There are individual items to assess surface pain severity, deep pain severity, and pain unpleasantness. The last item on the PQAS© asks participants to choose which of the three statements best describes their pain: variable, intermittent, or stable [31, 32].

Adult and Child Quality of Life

QOL was assessed through the Pediatric Quality of Life Inventory (PedsQL™) Generic Core Scales module 4.0 (English version) self-report questionnaire [33, 34]. The PedsQL™ assesses patient's perceptions of generic health-related quality of life with chronic health conditions [33, 34].

The PedsQL™ uses a 23-item questionnaire using the 0-4 Likert scale. Three versions were used: Adult (over 18), Teen (13-18), and Child (8 to 12). Each participant was provided with the appropriate questionnaire for his or her age. The PedsQL™ focuses on four domains of quality of life: Physical, Emotional, Social, and School/Work. These domains generate a composite score to assess overall QOL.

The PedsQL™ is a valid and reliable tool with internal consistency reliability for total QOL (alpha = 0.88 child, 0.86 adult), physical QOL (alpha = 0.80 child, 0.76 adult), psychosocial QOL (alpha = 0.83 child, 0.83 adult), emotional QOL (alpha = 0.73 child, 0.71 adult), social QOL (alpha = 0.71 child, 0.78 adult), and school/work QOL (alpha = 0.68 child, 0.75 adult) [30, 33-35]. The average scores in healthy children were 83 for total QOL, 84.41 for physical QOL, 82.38 for psychosocial QOL, 80.86 for emotional QOL, 87.42 for social QOL, 78.63 for school/work QOL [35]. The average scores in healthy adults were 78.18 for total QOL, 86.25 for physical QOL, 73.87 for psychosocial QOL, 66.68 for emotional QOL, 85.48 for social QOL, 69.47 for school/work QOL [34].

For ease of interpretation of the PedsQL™, score items are reverse scored and linearly transformed from 0-4 to a 0-100 scale (0=100, 1=75, 2=50, 3=25, 4=0), meaning that higher scores closer to 100 indicates better quality of life. A subscore of 0-100 can be calculated for each domain and score of 0-100 for the overall Total Scale Score. The Physical Functioning subscale score is reported as the Physical Health Summary Score. The Psychosocial Health Summary Score equals the sum of the items divided by the number of items answered on the Emotional, Social, and School/Work Functioning subscales. The Total Scale Score is the average of all of the items. For the purposes of this study, this survey will be referred to as the QOL survey.

Pain Management Questionnaire

The final tool used was a questionnaire to assess pain management techniques used by participants (Appendix D). If the participant was under the age of 18, the parent was asked to assist their child in completing the survey.

The questionnaire consisted of two questions. The first question asked the participants to report any pain management techniques that had helped to relieve or reduce their pain. The possible responses included physical therapy, exercise, pain medication, none, or other. If the participant answered other, they were asked to specify. The second question asked the participants to report which pain management technique best relieved or reduce their pain. The possible responses included physical therapy, exercise, pain medication, none, or other. If the participant answered other, they were asked to specify.

The amount of pain management techniques reported was also collected by counting the number of techniques used by each subject. The amount of techniques used may indicate that pain management techniques are not effective for an individual.

2.1.6 Survey Distribution

Survey distribution began in February 2014. Surveys were sent to participants by mail. Participants were asked to return the surveys within two weeks of receiving the materials.

2.1.7 Statistical Analyses

For assessing demographic information, descriptive statistics and frequencies were used. For continuous data, correlations and linear regressions were computed. Statistical analysis was carried out using IBM SPSS Statistics version 22.

3.0 RESULTS

3.1 DESCRIPTIVES

3.1.1 Entire Sample

Subjects were adults (n = 23) and children (n = 7) between the ages of 13 and 58 with 30 total participants. The sample consists of males (n = 5) and females (n = 25) with an average age of 27.27 (SD ± 12.7) years. All participants completed an age-appropriate QOL survey and the Pain Management questionnaire. Sample characteristics including ranges, means, and standard deviations were calculated for age, QOL, and pain management amount (Table 2).

The first set of variables was from the PedsQL QOL questionnaire. The mean total QOL score was 52.39 (SD ± 18.43). The mean scores for the subscales physical QOL and psychosocial QOL were 43.65 (SD ± 27.21) and 56.28 (SD ± 17.1) respectively. The mean scores of the components of psychosocial QOL were 53.33 (SD ± 16.21) for emotional QOL, 67.67 (SD ± 17.12) for social QOL, and 50.17 (SD ± 26.11) for school/work QOL.

The total amount of pain management techniques used ranged from 0 to 8, with a mean of 3.2 (SD ± 2.27).

Table 2: Descriptives for age, QOL and pain management amount in all subjects

	M (SD)	Range
Age	27.27 (12.70)	13 - 58
Total QOL	52.39 (18.43)	21.74 - 86.96
Physical QOL	43.65 (27.21)	0.13 – 100
Psychosocial QOL	56.28 (17.1)	23.33 - 90
Emotional QOL	53.33 (16.21)	20 - 85
Social QOL	67.67 (17.12)	20 - 100
School/Work QOL	50.17 (26.11)	0 - 90
Pain Management Amount	3.2 (2.27)	0 - 8

Sample frequencies were calculated for sex, diagnosis, and pain management use (Table 3). The sample population was 83.3% (n = 25) female and 16.7% (n = 5) male. About 36.7% (n = 11) have a clinical diagnosis of EDS, while 63.3% (n = 19) have a suspected EDS diagnosis, thus labeled as UCTD. Of this sample, 85.7% (n = 26) used some type of pain management.

Table 3: Frequencies of sex, diagnosis, and pain management use in all subjects

Sex	
Female	83.3% (n = 25)
Male	16.7% (n = 5)
Diagnosis	
Clinical EDS Diagnosis	36.7% (n = 11)
Suspected EDS	63.3% (n =19)
Pain Management Use	
Yes	85.7% (n = 26)
No	14.3% (n = 4)

3.1.2 Adult Sample

Subjects were adults (n = 23) between the ages of 18 and 58. The adult sample consists of male (n = 1) and female (n = 22) subjects with an average age of 30.87 (SD ± 12.4) years. These participants completed the PQAS©, PedsQL™ QOL suvey, and the Pain Management questionnaires. Sample characteristics including ranges, means, and standard deviations were calculated for age, pain, QOL, and pain management amount (Table 4).

The first set of variables was from the PQAS© pain questionnaire. The mean total pain score was 4.11 (SD ± 1.72), with a mean of 4.14 (SD ± 2.29), 3.56 (SD ± 1.68), and 4.71 (SD ± 2.19) for paroxysmal pain, surface pain, and deep pain respectively. The mean score for pain severity was 3.3 (SD ± 2.38) for surface pain and 6.61 (SD ± 2.93) for deep pain. The mean for overall pain unpleasantness was 6.39 (SD ± 2.74).

The next set of variables was from the PedsQL™ QOL questionnaire. The mean total QOL score was 48.44 (SD ± 17.73). The mean scores for the subscales physical QOL and psychosocial QOL were 36.82 (SD ± 24.14) and 53.62 (SD ± 17.69) respectively. The mean scores of the components of psychosocial QOL were 52.39 (SD ± 16.8) for emotional QOL, 65.65 (SD ± 18.36) for social QOL, and 45.87 (SD ± 16.05) for school/work QOL.

The total amount of pain management techniques used ranged from 0 to 8, with a mean of 3.2 (SD ± 2.27).

The last variable is from the pain management questionnaire. The total amount of pain management techniques used ranged from 0 to 8, with a mean of 3.3 (SD ± 2.44).

Table 4: Descriptives for age, pain, QOL and pain management amount in adult subjects

	M (SD)	Range
Age	30.87 (12.4)	18 - 58
Total Pain	4.11 (1.72)	0 – 6.45
Paroxysmal Pain	4.14 (2.29)	0 – 9.2
Surface Pain	3.56 (1.68)	0 - 6.4
Deep Pain	4.71 (2.19)	0 - 8.6
Pain Unpleasantness	6.39 (2.74)	0 - 10
Surface Pain Severity	3.3 (2.38)	0 - 8
Deep Pain Severity	6.61 (2.93)	0 - 10
Total QOL	48.44 (17.73)	21.74 – 86.96
Physical QOL	36.82 (24.18)	0.13 – 93.75
Psychosocial QOL	53.62 (17.69)	23.33 – 90.0
Emotional QOL	52.39 (16.8)	20 - 85
Social QOL	65.65 (18.36)	20 - 100
School/Work QOL	45.87 (26.05)	0 - 85
Pain Management Amount	3.3 (2.44)	0 - 8

Sample frequencies were calculated for sex, diagnosis, pain management use, and pain classification (Table 5). The sample population was 95.7% (n = 22) female and 4.3% (n = 1) male. About 30.4% (n = 7) have a confirmed diagnosis of EDS, while 63.3% (n = 16) have a suspected EDS diagnosis. Of this sample, 82.6% (n = 19) used some type of pain management. About 78.3% (n = 18) reported that their pain was variable on the pain classification question from the PQAS©.

Table 5: Frequencies for sex, diagnosis, and pain management use in adult subjects

Sex	
Female	95.7% (n = 22)
Male	4.3% (n = 1)
Diagnosis	
Clinical EDS Diagnosis	30.4% (n = 7)
Suspected EDS	69.6% (n =16)
Pain Management Use	
Yes	82.6% (n = 19)
No	17.4% (n = 4)

3.1.3 Child Sample

Child subjects (n = 7) consist of males (n = 4) and females (n = 3) between the ages of 13 and 18. These participants completed the PedsQL™ Pediatric Pain Questionnaire ™, PedsQL™ QOL survey, and the Pain Management questionnaire. Sample ranges for the child subjects were calculated for age, pain, QOL, and pain management amount (Table 6).

Table 6: Ranges for age, pain, QOL and pain management amount in child subjects

	Range
Age	13 - 17
Present Pain	0 - 6
Worst Pain	0 - 10
Total QOL	35.87 – 83.7
Physical QOL	21.88 – 100
Psychosocial QOL	43.33 – 78.33
Emotional QOL	35 - 80
Social QOL	55 - 90
School/Work QOL	20 - 90
Pain Management Amount	0 - 4

The ranges were calculated for sex, pain management use, and diagnosis in the child subjects (Table 7). The sample population had three females and four males. Of this sample, six used some type of pain management, while one did not use any. A diagnosis was confirmed in four subjects, while the remaining three have a suspected diagnosis.

Table 7: Frequencies for sex, diagnosis, and pain management use in child subjects

Sex	
Female	n = 4
Male	n = 3
Pain Management Use	
Yes	n = 6
No	n = 1
Diagnosis	
Confirmed EDS Diagnosis	n = 4
Suspected EDS	n = 3

3.2 CHARACTERIZATION OF PAIN

3.2.1 Pain in Adult Subjects

The PQAS© (Appendix D) asks subjects to report which type of pain best describes their pain. Intermittent pain is defined as pain that "comes and goes." Variable pain is defined as pain that "vary from one moment to the next," but these individuals are "never pain free." Stable pain is defined as pain that "does not change that much from one moment to another." Participants were asked which of these three types best describes the pattern of their pain.

About 78.3% (n = 18) of the adult subjects reported that their pain was variable, 17.4% (n = 4) reported their pain as intermittent, and 4.3% (n = 1) reported pain as stable. These results are summarized in Table 8.

Table 8: Pain Classification in Adult Subjects

Pain Classification	
Stable	4.3% (n = 1)
Variable	78.3% (n = 18)
Intermittent	17.4% (n = 4)

3.2.2 Pain in Child Subjects

The PPQ ^{TM} (Appendix D) begins with an open-ended question that allows the participant to describe their pain. The questions states: "What words would you use to describe your pain or hurt?" All seven of the child subjects responded.

One of the themes that emerged in these responses was the description of the pain as aching. One participant responded with "aching" as the description of pain. Some other participants also reported acute and aching pain. One participant described the pain as:

> "Mostly aching with acute pain in my knees."

Another participant reported a similar theme of aching pain with additional acute pain in certain areas of the body:

> "It depends: some days I have pain from indigestion. Some days I have joint pain in my knees. Other days my forehead aches, and sometimes my shins ache from poor arch support."

Some subjects reported that pain did not interfere with their lives. One subject reported "none", while another subject reported that the pain was "unobtrusive."

Another subject reported that pain was variable and described pain as:

"Annoying, random, most of the time tolerable."

One subject was more descriptive in the response section. This subject said:

"Sometimes my insides feel like they're attacking each other. When my joints dislocate, it's like someone is sawing or stabbing the leg/arm/shoulder etc. Every day is a fight between me and my body."

The PPQ ™ also includes the outline of a human body and asks the subject to place an "X" on the drawing in every area that they were currently experiencing pain. The results are summarized in Figure 1. The areas where pain was reported were: knees (n = 3), back (n = 3), shoulders (n = 2), stomach (n = 2), head (n = 1), and hands (n = 1).

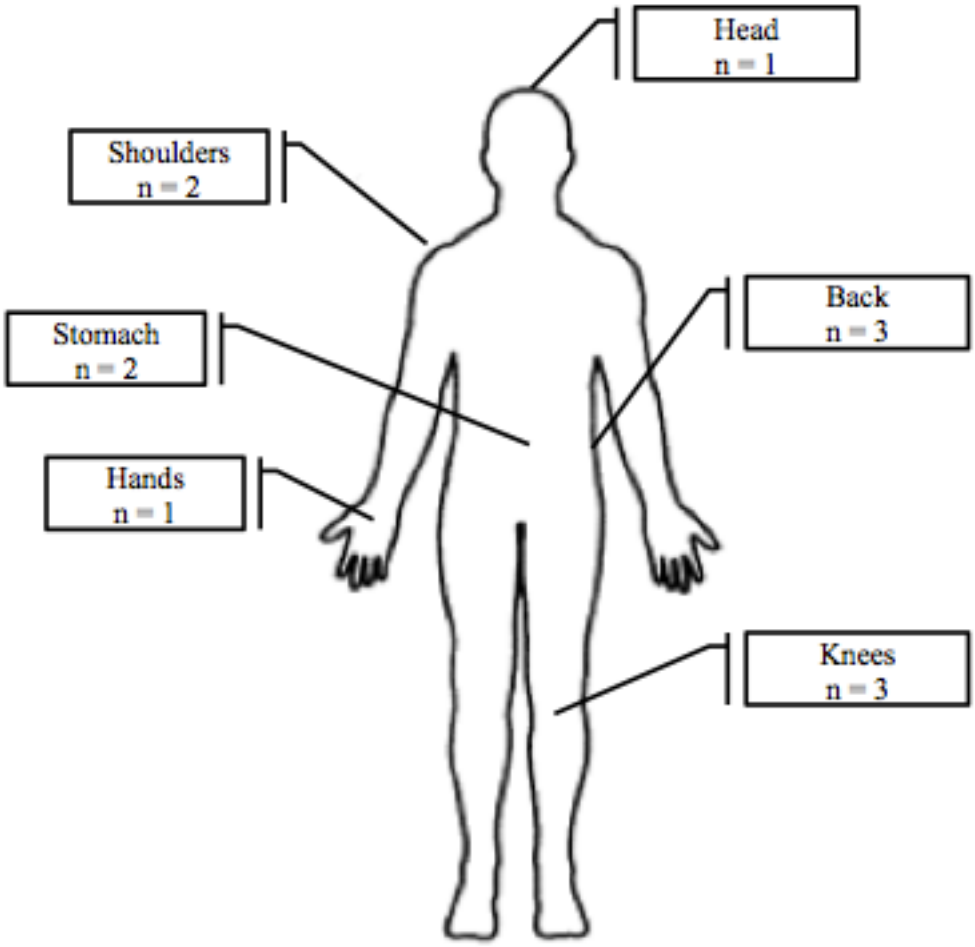

Figure 1: Areas of pain reported in child patients

3.3 PAIN MANAGEMENT

3.3.1 Pain Management in All Subjects

The number of subjects that reported each type of pain management is summarized in Figure 2. Physical therapy was used by 18 subjects and was recounted to be most effective by six subjects.

Exercise was reportedly used by 16 subjects and was reported to most effective by one subject. Pain medication was used by 24 subjects and was stated to be most effective by fourteen subjects. Other types of pain management were described by 19 subjects and reported to be most effective by ten of those individuals. The forms of pain management reported under "other" were: chiropractor (n = 5), massages (n = 4), rest (n = 4), heat (n = 4), ice/cold (n = 2), stretching (n = 2), surgeries (n =2), swimming (n = 2), acupuncture (n = 1), electrical stimulation (n = 1), homeopathic medicine (n = 1), injections in joints (n =1), pain counseling (n = 1), popping/putting bones in place (n = 1), and vodka (n = 1). Four subjects reported that they did not use any pain management techniques, and six reported that none of the pain management techniques they used were effective in treating their pain.

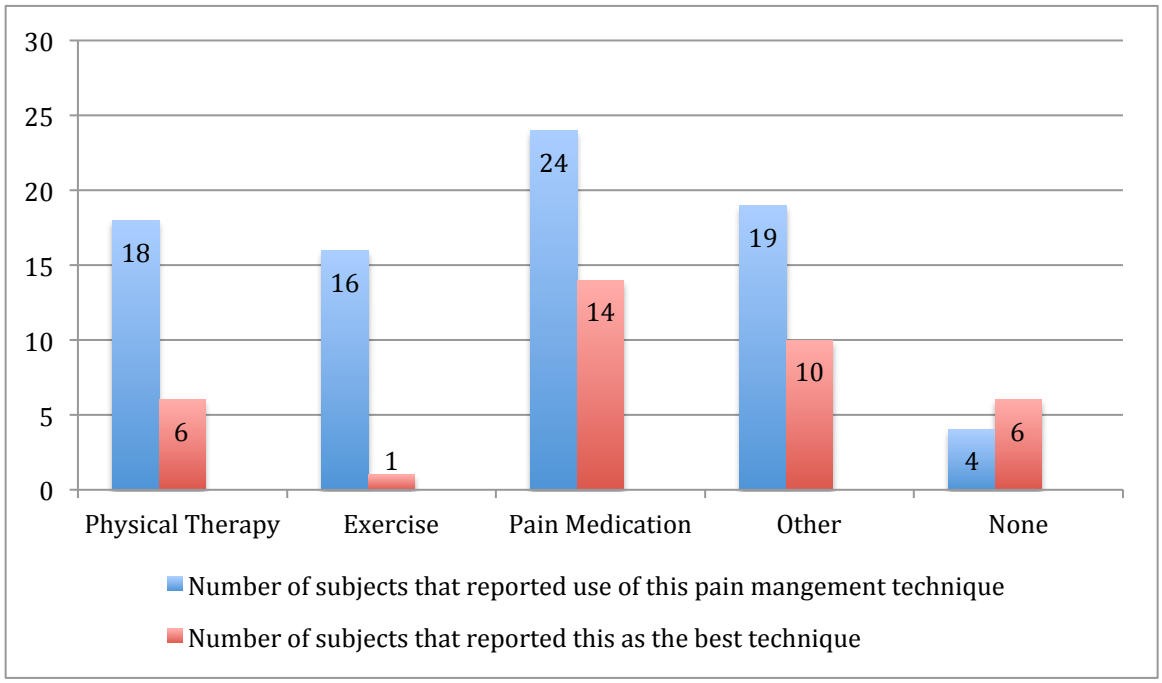

Figure 2: Types of pain management reported in all subjects

3.3.2 Pain Management in Adult Subjects

The number of adult subjects that reported each type of pain management is summarized in Figure 3. Physical therapy was used by 11 subjects and was recounted to be most effective by four subjects. Exercise was used by 16 subjects and reported to be effective by one subject. Pain medication was used by 18 subjects and was stated to be most effective by 11 subjects. Other types of pain management were used by 15 subjects and were most effective for nine subjects. The forms of pain management reported under "other" were: chiropractor (n = 4), massages (n = 3), rest (n = 3), heat (n = 3), ice/cold (n = 2), stretching (n = 2), surgeries (n =2), swimming (n = 2), acupuncture (n = 1), electrical stimulation (n = 1), homeopathic medicine (n = 1), injections in joints (n =1), pain counseling (n = 1), popping/putting bones in place (n = 1), and vodka (n = 1). Three subjects reported that they did not use any pain management techniques, and five reported that none of the pain management techniques used were most effective.

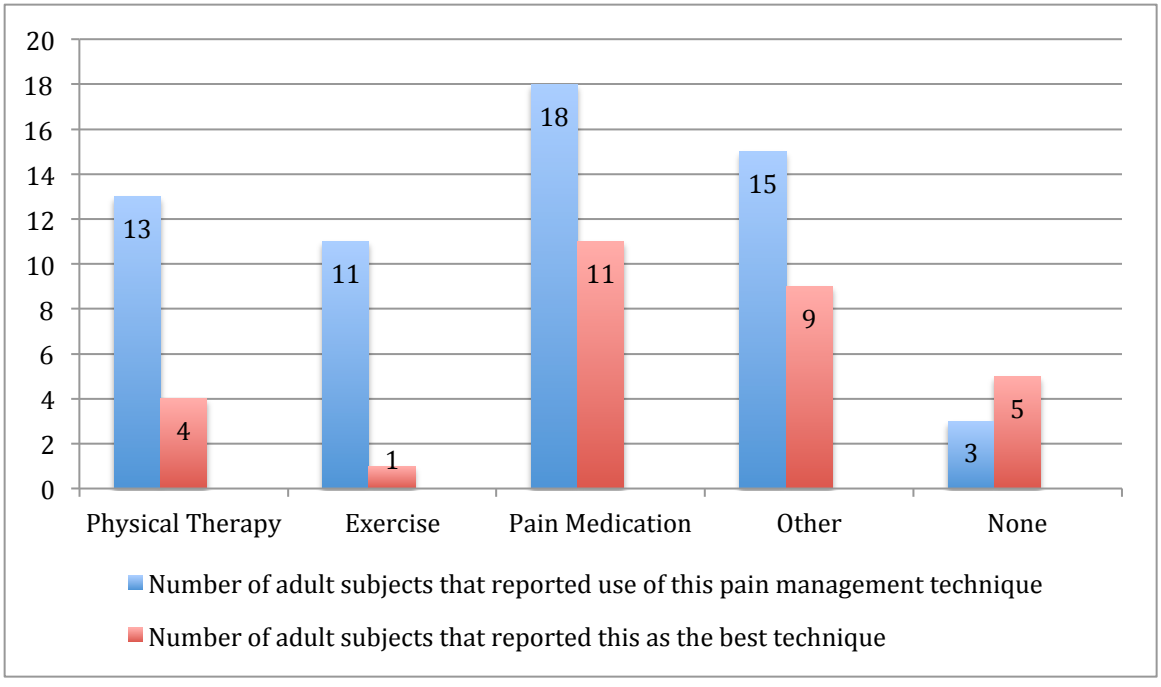

Figure 3: Types of pain management reported in adult subjects

3.3.3 Pain Management in Child Subjects

The number of child subjects that reported each type of pain management is summarized in Figure 4. Physical therapy was used by five subjects and was stated to be most effective by two subjects. Five subjects used exercise, but none of them found it to me the most effective type of pain management. Pain medication was used by six subjects and was reported to be most effective by three subjects. Other types of pain management were used by four subjects, but only one subject reported it to be the most effective pain management. The forms of pain management reported under "other" were: chiropractor (n = 1), heat (n = 1), massages (n = 1), and rest (n = 1). One child subject reported that no pain management techniques were used and none of the pain management techniques used were most effective

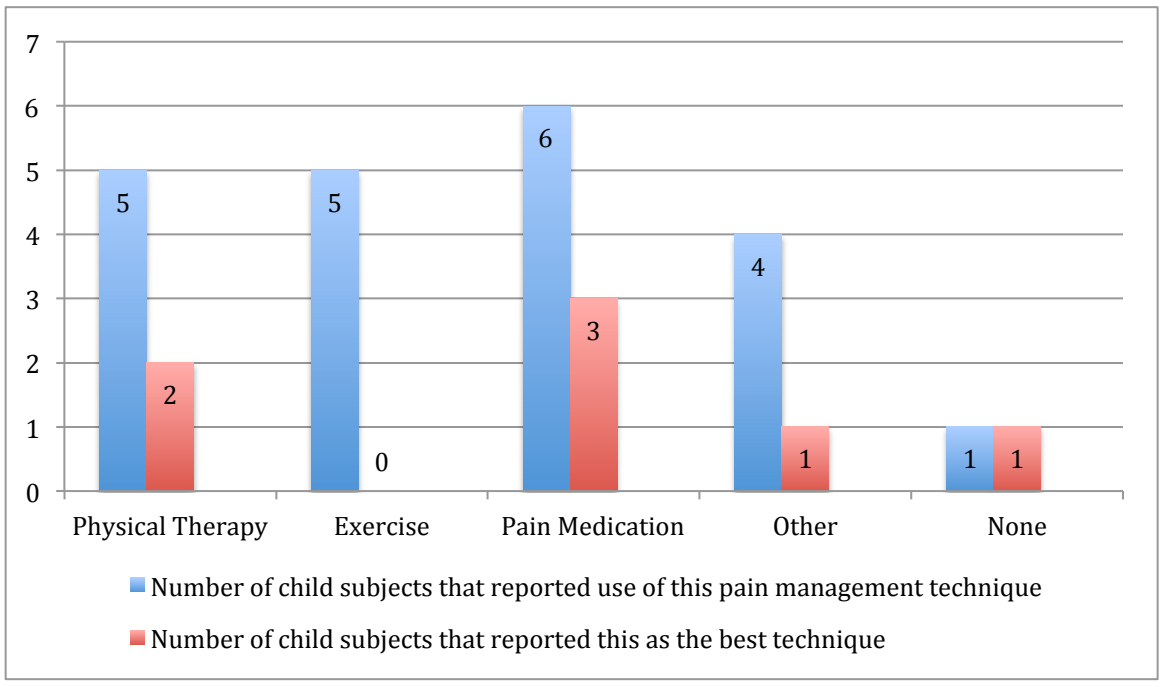

Figure 4: Types of pain management reported in child subjects

3.4 NORMALITY

The assumption of normality for total pain was testing using the Shapiro-Wilk test (SW =0.929, *df* =23, *p* = 0.103). These results and the Normal Q-Q plot of total pain (Figure 5) suggested that normality was reasonable.

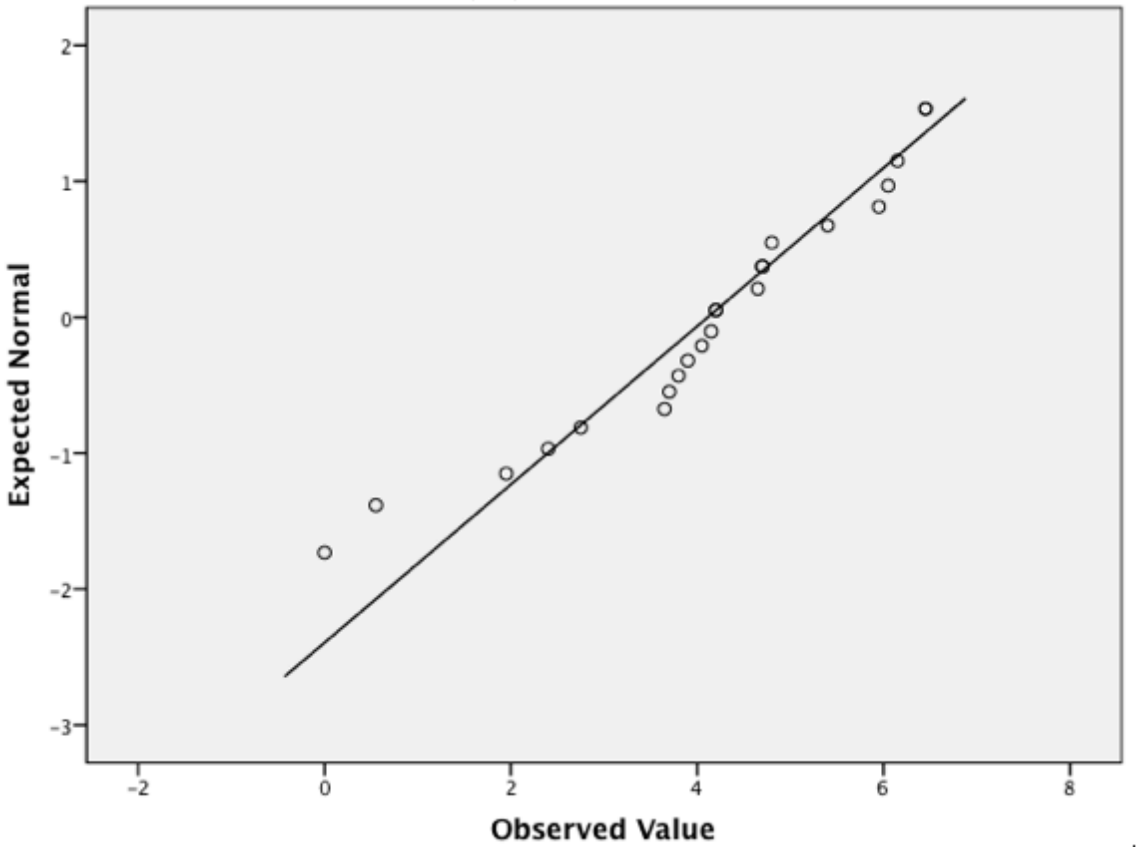

Figure 5: Normal Q-Q Plot for Total Pain

The assumption of normality for total QOL was tested using the Shapiro-Wilk test (SW =0.959, *df* = 23, *p* = 0.434). These results and the Normal Q-Q plot of total QOL (Figure 6) suggested that normality was reasonable.

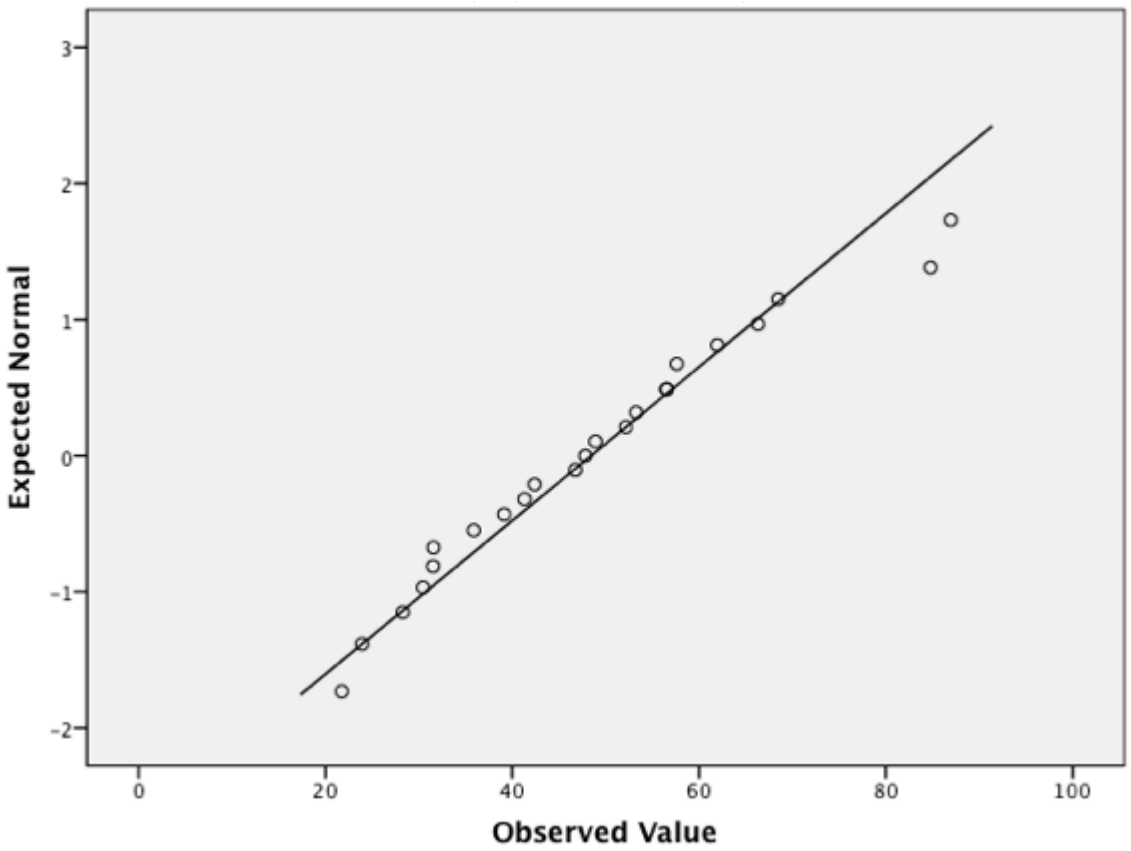

Figure 6: Normal Q-Q Plot for Total QOL

3.5 PAIN AND QOL IN ADULTS

Univariate linear regressions were performed to explore which types of pain are predictors of QOL. A model was generated for total QOL, physical QOL, psychosocial QOL, emotional QOL, social QOL, and school/work QOL. Each model included a pain quality variable as a predictor. Correlations were also performed to explore the relationships between pain variables and QOL variables (Table 9).

Table 9: Correlations for pain, QOL, and pain management amount

	Total QOL	Physical QOL	Psychosocial QOL	Emotional QOL	Social QOL	School/Work QOL	Pain Management Amount
Total Pain	-0.769**	-0.754**	-0.712**	-0.589**	-0.585**	-0.492*	0.318
Paroxysmal Pain	-0.664**	-0.664**	-0.618**	-0.468*	-0.469*	-0.547**	0.432*
Surface Pain	-0.668**	-0.621**	-0.710**	-0.686**	-0.668**	-0.397	0.181
Deep Pain	-0.631**	-0.616**	-0.556*	-0.472*	-0.458*	-0.411	0.340
Pain Unpleasantness	-0.727**	-0.773**	-0.458**	-0.277	-0.375	-0.374	0.450*
Surface Pain Severity	-0.447*	-0.398	-0.383	-0.421*	-0.218	-0.217	-0.095
Deep Pain Severity	-0.641**	-0.744**	-0.408**	-0.187	-0.316	-0.388	0.513*
Pain Management Amount	-0.367	-0.343	-0.355	0.087	-0.451*	-0.376	1

$p < 0.05$*, $p < 0.01$**

3.5.1 Pain and Total QOL

Univariate linear regressions were performed to explore which types of pain are predictors of total QOL (Table 10). All pain quality types were statistically significant predictors of total QOL except for surface pain severity.

Table 10: Univariate regression analyses for pain variables in predicting total QOL

Variable	β	R^2
Total Pain	-0.769**	0.591
Paroxysmal Pain	-0.692**	0.479
Surface Pain	-0.714**	0.510
Deep Pain	-0.624**	0.390
Pain Unpleasantness	-0.628**	0.394
Surface Pain Severity	-0.394	0.156
Deep Pain Severity	-0.587**	0.344

$p < 0.05$*, $p < 0.01$**

3.5.2 Pain and Physical QOL

Univariate linear regressions were performed to explore which types of pain are predictors of physical QOL (Table 11). All pain quality types were statistically significant predictors of physical QOL except for surface pain severity.

Table 11: Univariate regression analyses for pain variables in predicting physical QOL

Variable	β	R^2
Total Pain	-0.754**	0.569
Paroxysmal Pain	-0.664**	0.441
Surface Pain	-0.621**	0.386
Deep Pain	-0.616**	0.379
Pain Unpleasantness	-0.773**	0.598
Surface Pain Severity	-0.398	0.159
Deep Pain Severity	-0.744**	0.554

$p < 0.05$*, $p < 0.01$**

3.5.3 Pain and Psychosocial QOL

Univariate linear regressions were performed to explore which types of pain are predictors of psychosocial QOL (Table 12). All pain quality types were statistically significant predictors of psychosocial QOL except for surface pain severity and deep pain severity.

Table 12: Univariate regression analyses for pain variables in predicting psychosocial QOL

Variable psychosocial	β	R^2
Total Pain	-0.712**	0.508
Paroxysmal Pain	-0.618**	0.381
Surface Pain	-0.710**	0.504
Deep Pain	-0.556**	0.309
Pain Unpleasantness	-0.458*	0.210
Surface Pain Severity	-0.383	0.147
Deep Pain Severity	-0.408	0.166

$p < 0.05$*, $p < 0.01$**

3.5.4 Pain and Emotional QOL

Univariate linear regressions were performed to explore which types of pain are predictors of emotional QOL (Table 13). All pain quality types were statistically significant predictors of emotional QOL except for deep pain severity and pain unpleasantness.

Table 13: Univariate regression analyses for pain variables in predicting emotional QOL

Variable	β	R^2
Total Pain	-0.589**	0.347
Paroxysmal Pain	-0.468*	0.219
Surface Pain	-0.686**	0.471
Deep Pain	-0.472*	0.223
Pain Unpleasantness	-0.277	0.077
Surface Pain Severity	-0.421*	0.177
Deep Pain Severity	-0.187	0.035

$p < 0.05$*, $p < 0.01$**

3.5.5 Pain and Social QOL

Univariate linear regressions were performed to explore which types of pain are predictors of social QOL (Table 14). All pain quality types were statistically significant predictors of social QOL except for pain unpleasantness, surface pain severity, and deep pain severity.

Table 14: Univariate regression analyses for pain variables in predicting social QOL

Variable	β	R^2
Total Pain	-0.585**	0.342
Paroxysmal Pain	-0.469*	0.220
Surface Pain	-0.668**	0.446
Deep Pain	-0.458*	0.209
Pain Unpleasantness	-0.375	0.141
Surface Pain Severity	-0.218	0.047
Deep Pain Severity	-0.316	0.100

$p < 0.05$*, $p < 0.01$**

3.5.6 Pain and School/Work QOL

Univariate linear regressions were performed to explore which types of pain are predictors of school/work QOL (Table 15). The only pain quality type that was a statistically significant predictor of school/work QOL was paroxysmal pain.

Table 15: Univariate regression analyses for pain variables in predicting school/work QOL

Variable school/work	β	R^2
Total Pain	-0.492*	0.242
Paroxysmal Pain	-0.547**	0.299
Surface Pain	-0.397	0.158
Deep Pain	-0.411	0.169
Pain Unpleasantness	-0.374	0.140
Surface Pain Severity	-0.217	0.047
Deep Pain Severity	-0.388	0.150

$p < 0.05$*, $p < 0.01$**

3.6 PAIN, QOL, AND PAIN MANAGEMENT USE

Multiple regression analysis was performed to explore predictors for the outcome of QOL. A model was generated for total QOL, physical QOL, psychosocial QOL, emotional QOL, social QOL, and school/work QOL. Each model included a pain variable and a pain management variable had a significant effect on QOL.

3.6.1 Pain, Total QOL, and Pain Management Use

Multiple linear regressions were performed to explore predictors of total QOL and the results are summarized in Table 16. Surface pain severity and pain management amount were both statistically significant predictors of total QOL.

Table 16: Multiple regression analyses for predicting total QOL

Dependent Variable	Independent Variables	β	F - Value	R^2
Total QOL	Total Pain Pain Management Use	-0.761** -0.027	14.470**	0.591
	Paroxysmal Pain Pain Management Use	-0.689** -0.011	9.197**	0.479
	Surface Pain Pain Management Use	-0.696** -0.078	10.634**	0.515
	Deep Pain Pain Management Use	-0.610** -0.044	6.427**	0.391
	Pain Unpleasantness Pain Management Use	-0.610** -0.169	7.317**	0.423
	Surface Pain Severity Pain Management Use	-0.373 -0.195	2.391	0.193
	Deep Pain Severity Pain Management Use	-0.569** -0.180	6.036**	0.376
	Total Pain Pain Management Amount	-0.725** -0.136	15.462**	0.607
	Paroxysmal Pain Pain Management Amount	-0.656** -0.083	9.402**	0.485
	Surface Pain Pain Management Amount	-0.669** -0.245	13.125**	0.568
	Deep Pain Pain Management Amount	-0.565** -0.174	7.134**	0.416
	Pain Unpleasantness Pain Management Amount	-0.581** -0.105	6.758**	0.403
	Surface Pain Severity Pain Management Amount	-0.433* -0.408*	4.710*	0.320
	Deep Pain Severity Pain Management Amount	-0.541* -0.089	5.388*	0.350

$p < 0.05$*, $p < 0.01$**

3.6.2 Pain, Physical QOL, and Pain Management Use

Multiple linear regressions were performed to explore predictors of physical QOL and the results are summarized in Table 17. Both predictors were not statistically significant in any of the models.

Table 17: Multiple regression analyses for predicting physical QOL

Dependent Variable	Independent Variables	β	F - Value	R^2
Physical QOL	Total Pain Pain Management Use	-0.798** 0.159	14.530**	0.592
	Paroxysmal Pain Pain Management Use	-0.722** 0.177	8.821**	0.469
	Surface Pain Pain Management Use	-0.641** 0.086	6.473**	0.393
	Deep Pain Pain Management Use	-0.662** 0.149	6.641**	0.399
	Pain Unpleasantness Pain Management Use	-0.776** 0.027	14.906**	0.598
	Surface Pain Severity Pain Management Use	-0.397 -0.015	1.890	0.159
	Deep Pain Severity Pain Management Use	-0.746** 0.014	12.433**	0.554
	Total Pain Pain Management Amount	-0.718** -0.115	13.845**	0.581
	Paroxysmal Pain Pain Management Amount	-0.634** -0.069	8.005**	0.445
	Surface Pain Pain Management Amount	-0.578** -0.238	7.881**	0.441
	Deep Pain Pain Management Amount	-0.564** -0.151	6.641**	0.399
	Pain Unpleasantness Pain Management Amount	-0.776** 0.007	14.865**	0.598
	Surface Pain Severity Pain Management Amount	-0.435* -0.384	4.386*	0.305
	Deep Pain Severity Pain Management Amount	-0.771** 0.053	12.527**	0.556

$p < 0.05$*, $p < 0.01$**

3.6.3 Pain, Psychosocial QOL, and Pain Management Use

Multiple linear regressions were performed to explore predictors of psychosocial QOL and the results are summarized in Table 18. Surface pain severity and pain management amount were both statistically significant predictors of psychosocial QOL.

Table 18: Multiple regression analyses for predicting psychosocial QOL

Dependent Variable	Independent Variables	β	F - Value	R^2
Psychosocial QOL	Total Pain Pain Management Use	-0.668** -0.163	11.379**	0.532
	Paroxysmal Pain Pain Management Use	-0.565** -0.162	6.800**	0.405
	Surface Pain Pain Management Use	-0.665** -0.196	11.735**	0.540
	Deep Pain Pain Management Use	-0.497* -0.190	5.196*	0.342
	Pain Unpleasantness Pain Management Use	-0.426* -0.299	4.255*	0.298
	Surface Pain Severity Pain Management Use	-0.350 -0.308	3.165	0.240
	Deep Pain Severity Pain Management Use	-0.378 -0.309	3.529*	0.261
	Total Pain Pain Management Amount	-0.667** -0.143	11.093**	0.526
	Paroxysmal Pain Pain Management Amount	-0.571** -0.108	6.419**	0.391
	Surface Pain Pain Management Amount	-0.667** -0.234	12.552**	0.577
	Deep Pain Pain Management Amount	-0.492* -0.187	5.160*	0.340
	Pain Unpleasantness Pain Management Amount	-0.374 -0.186	3.119	0.238
	Surface Pain Severity Pain Management Amount	-0.421* -0.395*	4.314*	0.301
	Deep Pain Severity Pain Management Amount	-0.306 -0.198	2.424	0.195
	Surface Pain Severity Pain Management Amount	-0.435* -0.384	4.386*	0.305
	Deep Pain Severity Pain Management Amount	-0.771** 0.053	12.527**	0.556

$p < 0.05$*, $p < 0.01$**

3.6.4 Pain, Emotional QOL, and Pain Management Use

Multiple linear regressions were performed to explore predictors of emotional QOL and the results are summarized in Table 19. Both predictors were not statistically significant in any of the models.

Table 19: Multiple regression analyses for predicting emotional QOL

Dependent Variable	Independent Variables	β	F - Value	R^2
Emotional QOL	Total Pain Pain Management Use	-0.585** -0.017	5.237**	0.348
	Paroxysmal Pain Pain Management Use	-0.459* -0.027	2.817	0.220
	Surface Pain Pain Management Use	-0.681** -0.024	8.915**	0.471
	Deep Pain Pain Management Use	-0.462* -0.032	2.885	0.224
	Pain Unpleasantness Pain Management Use	-0.261 -0.148	1.093	0.098
	Surface Pain Severity Pain Management Use	-0.407 -0.133	2.417	0.195
	Deep Pain Severity Pain Management Use	-0.171 -0.160	0.644	0.060
	Total Pain Pain Management Amount	-0.686** 0.305	7.567**	0.431
	Paroxysmal Pain Pain Management Amount	-0.622** 0.355	4.745*	0.322
	Surface Pain Pain Management Amount	-0.726** 0.218	10.694**	0.517
	Deep Pain Pain Management Amount	-0.567* 0.280	4.127*	0.292
	Pain Unpleasantness Pain Management Amount	-0.396 0.265	1.530	0.133
	Surface Pain Severity Pain Management Amount	-0.417 0.047	2.187	0.179
	Deep Pain Severity Pain Management Amount	-0.314 0.248	0.872	0.080

$p < 0.05$*, $p < 0.01$**

3.6.5 Pain, Social QOL, and Pain Management Use

Multiple linear regressions were performed to explore predictors of social QOL and the results are summarized in Table 20. Surface pain and pain management amount were both statistically significant predictors of social QOL.

Table 20: Multiple regression analyses for predicting social QOL

Dependent Variable	Independent Variables	β	F - Value	R^2
Social QOL	Total Pain Pain Management Use	-0.533** -0.189	6.007**	0.375
	Paroxysmal Pain Pain Management Use	-0.403 -0.203	3.458	0.257
	Surface Pain Pain Management Use	-0.624** -0.194	9.282**	0.481
	Deep Pain Pain Management Use	-0.391 -0.212	3.332	0.250
	Pain Unpleasantness Pain Management Use	-0.343 -0.297	2.956	0.228
	Surface Pain Severity Pain Management Use	-0.183 -0.315	1.700	0.145
	Deep Pain Severity Pain Management Use	-0.286 -0.307	2.390	0.193
	Total Pain Pain Management Amount	-0.491* -0.295	7.257**	0.431
	Paroxysmal Pain Pain Management Amount	-0.337 -0.306	4.203*	0.296
	Surface Pain Pain Management Amount	-0.606** -0.342*	12.651**	0.559
	Deep Pain Pain Management Amount	-0.344 -0.334	4.453*	0.308
	Pain Unpleasantness Pain Management Amount	-0.216 -0.354	3.173	0.241
	Surface Pain Severity Pain Management Amount	-0.263 -0.476*	3.740*	0.272
	Deep Pain Severity Pain Management Amount	-0.114 -0.393	2.711	0.213

$p < 0.05$*, $p < 0.01$**

3.6.6 Pain, School/Work QOL, and Pain Management Use

Multiple linear regressions were performed to explore predictors of school/work QOL and the results are summarized in Table 21. Both predictors were not statistically significant in any of the models.

Table 21: Multiple regression analyses for predicting school/work QOL

Dependent Variable	Independent Variables	β	F - Value	R^2
School/Work QOL	Total Pain Pain Management Use	-0.443* -0.178	3.727*	0.272
	Paroxysmal Pain Pain Management Use	-0.503* -0.136	4.612*	0.316
	Surface Pain Pain Management Use	-0.348 -0.221	2.568	0.204
	Deep Pain Pain Management Use	-0.352 -0.189	2.522	0.201
	Pain Unpleasantness Pain Management Use	-0.345 -0.262	2.617	0.207
	Surface Pain Severity Pain Management Use	-0.186 -0.279	1.416	0.124
	Deep Pain Severity Pain Management Use	-0.362 -0.264	2.812	0.141
	Total Pain Pain Management Amount	-0.414* -0.245	4.202*	0.296
	Paroxysmal Pain Pain Management Amount	-0.473* -0.172	4.777*	0.323
	Surface Pain Pain Management Amount	-0.340 -0.315	3.400	0.254
	Deep Pain Pain Management Amount	-0.320 -0.267	3.026	0.232
	Pain Unpleasantness Pain Management Amount	-0.257 -0.261	2.408	0.194
	Surface Pain Severity Pain Management Amount	-0.255 -0.401	2.594	0.206
	Deep Pain Severity Pain Management Amount	-0.264 -0.241	2.393	0.193

$p < 0.05$*, $p < 0.01$**

3.7 OTHER FACTORS RELATED TO PAIN AND QOL

Univariate linear regressions were performed to explore which if age, sex, or pain management were predictors of QOL in all subjects. A model was generated for total QOL, physical QOL, psychosocial QOL, emotional QOL, social QOL, and school/work QOL.

3.7.1 Age and QOL

Univariate linear regressions were performed to explore which if age is a predictor of QOL (Table 22). Age was a statistically significant predictor of physical QOL.

Table 22: Univariate regression analysis for age and QOL

Dependent Variable	Independent Variable	β	R^2
Total QOL	Age	-0.533	0.375
Physical QOL	Age	-0.412*	0.170
Psychosocial QOL	Age	-0.624	0.481
Emotional	Age	-0.391	0.250
Social QOL	Age	-0.343	0.228
School/Work QOL	Age	-0.183	0.145

$p < 0.05$*, $p < 0.01$**

3.7.2 Sex and QOL

Univariate linear regressions were performed to explore if sex was a predictors of QOL (Table 23). Sex was not a predictor of QOL.

Table 23: Univariate regression analysis for sex and QOL

Dependent Variable	Independent Variable	β	R^2
Total QOL	Sex	-0.533	0.375
Physical QOL	Sex	-0.412	0.170
Psychosocial QOL	Sex	-0.624	0.481
Emotional	Sex	-0.391	0.250
Social QOL	Sex	-0.343	0.228
School/Work QOL	Sex	-0.183	0.145

$p < 0.05$*, $p < 0.01$**

3.7.3 Pain Management and QOL

Amount of pain management techniques used relates to social QOL. To assess the relationship between the amount of pain management techniques used and social QOL, linear regression was used and the result is shown below in Table 24. The prediction model was statistically

significant $F_{1, 28} = 7.666$, $p < 0.05$, and accounted for about 21.5% percent of the total variance ($R^2 = 0.215$) of social QOL. The more pain management techniques used, the lower the social quality of life. The predictor of pain unpleasantness, $\beta = -0.464$, $p < 0.05$, had a significant effect on social QOL.

Table 24: Regression analysis for pain management amount and social QOL

Variable	β
Pain Management Amount	-0.464*

$R^2 = 0.215$ $p < 0.05$*, $p < 0.01$**

4.0 DISCUSSION

4.1 AIM 1: CHARACTERIZATION OF PAIN IN EDS AND UCTD

Looking at the subjects in the current study, there were many differences in the pain reported. There was a wide variability of types and severity of pain reported across this small and possibly unrepresentative sample.

In the adult population, the scores for all pain qualities had large ranges with some subjects reporting pain as low as zero and some reporting pain as high as ten. The average pain scores were highest for pain unpleasantness and deep pain severity. The majority of adult subjects (78.3%) reported that their pain was variable, which is defined as pain that varies in type and severity, but is constant [31]. This report confirms previous findings in the literature that a large majority of individuals with EDS experience chronic pain that varies in degree [14]

In the child population, the scores for present pain ranged from zero to six and scores for worst pain ranged from zero to ten. The areas where pain was reported in the children also varied. Three subjects reported pain in their knees and three reported pain in their back. Two participants also labeled the shoulders and stomach as areas where pain was experienced. One subject reported to have pain in the head and hands. Previous literature has reported that the most frequent localization of pain was the neck, hips, shoulders, forearms, and legs, whereas

abdominal pain and headaches were reported much more infrequently [14]. The results of this study differ, however the earlier studies only included adults with EDS.

The open-ended question from the child pain survey also revealed more descriptive qualities of pain. There was a theme in the responses of "aching" pain and "acute" pain. Also, some participants referred to pain as "annoying", but "most of the time tolerable." Some respondents answered with "none" or described pain as "unobtrusive." On the other hand, one participant described pain in much more detail and expressed that the pain was more severe than the other subjects. This participant reported that: "my insides feel like they're attacking each other." The subject also reported joint dislocations and that this process feels as if "someone is sawing or stabbing" the joint. The subject concluded the response by saying that "every day is a fight between me and my body." This last statement implies a considerably decreased quality of life. Some of the previous literature has included similar pain themes, such as cutting, nagging, tiring, troublesome, sickening [14].

There is pain reported across this small sample, with type and severity fluctuating between individuals. Some individuals reported experiencing no pain, while others clearly had severe pain that affected their quality of life. In this sample, the findings suggest that individuals with EDS and UCTD experience wide variability in the type and severity of their pain.

4.2 AIM 2: PAIN MANAGEMENT USED IN EDS AND UCTD

Pain management was commonly used in this sample, with the type of techniques used differing greatly across the entire sample.

The majority (85.7%) of the entire sample reported using some type of pain management. First, 24 (80%) subjects reported the use of pain medication, which was the most reported response. Most of those individuals (14) indicated that pain medication was the most effective treatment. This confirms previous literature that reported that pain medication was used by about 89% of the individuals with EDS surveyed [14]. Interestingly, there were 16 reports of exercise as a pain management technique, however only one subject reported exercise to be the most effective technique.

Of the management that the subjects reported under "other", the most popular choice was going to a chiropractor for manipulation (5), followed by massage (4), rest (4), heat (4), cold (2), stretching (2), surgeries (2), and swimming (2). Only one individual reported the use of each of the following management: acupuncture, electrical stimulation, homeopathic medicine, injections in joints, pain counseling, putting bones back in place, and vodka. Interestingly enough, only one person reported the use of controlled substances. This may be because the individuals did not want to report the use of controlled or illegal drugs for the purposes of this study.

These results are similar to those reported in the literature for other chronic pain syndromes. A previous study has reported that pain medication, rest, heat, and exercise were the methods used most by individuals with rheumatoid arthritis [36]. The most helpful were pain medication, rest and heat [36]. However, the number of pain management techniques used was increased in younger individuals with rheumatoid arthritis, which is not something that was noted in this study [36]. This may be explained by the differences in the natural history of the two conditions.

Pain management use is reported across this small sample, with the type of technique used widely varying between individuals. The findings from this sample suggest that individuals with EDS and UCTD may use many different techniques to manage their pain. The findings also suggest that exercise may not be effective for most of these individuals, however further study with a larger sample is needed to confirm.

4.3 AIM 3: RELATIONSHIP BETWEEN PAIN AND QOL

As expected, this study indicates that increased pain is very strongly associated with decreased quality of life in this population. Almost every pain quality was a statistically significant predictor of quality of life. This confirms the data found from previous studies that indicated this relationship exists when there is chronic pain in EDS populations and other chronic pain syndromes [6, 21, 37, 38].

Another related finding was that increased amount of pain management techniques used and increased surface pain had a statistically significant effect on social QOL. This relationship was not identified in any other type of pain or QOL. A possible explanation is that pain management is less effective for treating surface pain, therefore these individuals must use more pain management techniques to help relieve their discomfort. Potentially, pain management may be more effective at treating the other types of pain in this population (such as deep pain), since it does not appear to be suitable for relieving surface pain. This relationship does not exist with any of the other types of pain or subscales of quality of life.

4.4 AIM 4: RELATIONSHIPS OF OTHER FACTORS WITH QOL

One interesting finding was the statistically significant relationship between increased amounts of pain management techniques and decreased social quality of life in this sample. One potential explanation for this relationship is that more pain management may interfere with a person's daily life and logically could decrease a person's social QOL. Another possible explanation is that those who use more pain management techniques may have more severe pain, which would then impact their social lives and decrease their social QOL. Those who use more pain management techniques have significantly increased pain unpleasantness and deep pain severity. This could indicate an increased need for social support in individuals with EDS and UCTD

Age was also found to be a statically significant predicator of physical QOL in the entire sample. This result supports the claims in previous literature that the physical nature of this disease becomes more severe with age. [6]

Sex was not found to be a significant predictor of QOL. This may be explained by the small sample of males in the current study.

4.5 IMPLICATIONS FOR EDS AND UCTD

The main aim of this study was to assess the relationship between pain and quality of life in EDS and UCTD patients. By establishing this association, the effectiveness of pain management techniques can be analyzed to determine if they change the relationship. Determining which pain management techniques are most effective could help healthcare professionals to better

treat, manage, and possibly prevent the chronic pain that these individuals experience. Reducing or relieving pain in these individuals would hopefully increase their quality of life.

4.6 PUBLIC HEALTH SIGNIFICANCE

Since EDS and UCTD are not well-known conditions, there is very limited public knowledge about these conditions, even in the medical field. Many people have symptoms of connective tissue disorders, but may not know enough to seek an evaluation for these conditions. Clinical diagnosis is also subjective and may depend on the physician diagnosing the condition. Furthermore, many individuals with a clinical diagnosis of EDS are not able to confirm a diagnosis through molecular testing. Thus, connective tissue disorders often go undiagnosed much longer than other conditions due to these issues.

This study could also serve as a template for other conditions that involve chronic pain and decreased quality of life. If pain management techniques or other interventions could be implemented, this could vastly improve the quality of life in people who suffer from debilitating and disabling conditions.

4.7 LIMITATIONS

One limitation of this study was the small sample size of participants. The survey was sent to 125 patients and 30 surveys were returned. The study could have been much stronger if there were more participants, especially if there are more subtle relationships among the variables.

Having a few outliers could significantly alter the results of the study because there were a modest number of participants.

This may be another explanation as to why there were no significant findings for some variables. If there were a larger group of children and adults that participated, perhaps the relationships found would have been stronger and more relationships would have been statistically significant. At the same time, it should be noted that in the prior literature of EDS and UCTD patients, it is not uncommon to have group sizes as small as or smaller than the 30 participants in this study [6, 12, 16, 21, 37].

Another limitation is that the participants either have a clinical diagnosis of EDS that has not been confirmed genetically, or they have UCTD that is suspected to be EDS. The physician and healthcare providers that evaluate this patient in the genetics clinic make the distinction in diagnoses. This diagnosis can be subjective in determining if someone has a diagnosis of EDS or has some type of UCTD, but the type cannot always be determined by their symptoms due to the overlap in EDS types. This physician bias may also affect the results of this study.

Another limitation of this study is that we were unable to compare the children to the adults because different surveys were used. The PQAS© questionnaire used for adults was more complicated to allow for more descriptive and specific data. The PQAS© would likely be too confusing and advanced for most children to answer. The child pain surveys were much simpler and were targeted towards the age groups. One potential idea would be to give a simple pain survey to both adults and child patients. However, if the adults had received a much simpler survey, the more subtle relationships between certain pain qualities would be lost. If the same survey were to be used, the data would likely be limited to pain severity, frequency, and location.

Another limitation is the number of surveys received for the pediatric population. Only 6 were returned which did not give us enough data to analyze the relationships in the pediatric population. Potential explanations for this are that the pediatric patients are experiencing less pain than the adult populations. Also, the surveys of those under 18 were sent to the parents, so it is possible that the parents were not as motivated for their child to participate in this study.

Only one adult male returned the survey for the current study. This may be explained by the fact that of the 69 adults that were eligible for the study, only 14 of those were male. This is not an uncommon finding in previous studies as the majority of individuals with EDS are reportedly female, sometimes over 90% [6, 12, 14]. It is also possible that men in this population do not participate in research as much as females because they are not seeking a diagnosis or medical assistance. Potentially, the condition may affect them differently and they are not as motivated to seek medical help or a diagnosis.

4.8 FUTURE RESEARCH

The data in this study provided some information about pain, quality of life, and pain management in patients with EDS and UCTD. However, future research on CTD and pain would be beneficial to these patients.

It would be valuable to consider a longitudinal study of EDS or other CTD patients to determine if the relationship between pain and QOL changes over the lifetime. It would also be interesting to do studies on individuals before and after they have begun a type of pain management to determine more directly if their quality of life is improving. Additional variables could be evaluated to determine if there are any other factors that affect these relationships such

as the number of symptomatic years or number of dislocation events. Also, using genetic testing as a variable could be beneficial in determining if there are any genotype/phenotype correlations.

Another possible direction would be to change the way the data was collected. Very few surveys were sent back from the pediatric population compared to the adult population. A future study could involve in-person interviews or collecting the data verbally when a child presents to the clinic with EDS or UCTD. This would increase the response rate and increase the sample size.

APPENDIX A

IRB APRROVAL LETTER

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

To: Suneeta Madan-Khetarpal MD

From: Christopher Ryan PHD, Vice Chair

Date: 2/3/2014

IRB#: PRO13080515

Subject: Pain and quality of life in connective tissue disorder patients

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The University of Pittsburgh Institutional Review Board reviewed and approved the above referenced study by the expedited review procedure authorized under 45 CFR 46.110 and 21 CFR 56.110. Your research study was approved under:

45 CFR 46.110.(5)

45 CFR 46.110.(7)

The risk level designation is Minimal Risk.

Approval Date: 2/3/2014

Expiration Date: 2/2/2015

For studies being conducted in UPMC facilities, no clinical activities can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems, which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

APPENDIX B

RECRUITMENT LETTER

Children's Hospital of Pittsburgh of UPMC

To whom it may concern:

You/your child are eligible to participate in a research study for people who have a connective tissue disorder (CTD). The study is looking to see if pain affects the daily life of individuals with a CTD.

We are contacting you because you/your child:

1. Has a positive genetic test for a known connective tissue disorder gene (Ehlers-Danlos syndrome),

OR

2. Has been evaluated by one of the physicians in the Division of Medical Genetics at Children's Hospital of Pittsburgh of UPMC and given a diagnosis of CTD or mixed CTD.

Participation in this study involves you/your child answering survey questions. The survey will take 20 minutes of your time. If you are a parent of a child with a CTD, please help him/her in answering the questions. Some information about you/your child will be used from the medical record including: age, symptoms, and diagnosis. Participants must be between age 8 and 80.

If you would like to participate, please follow these instructions:

1. Review consent form
2. Sign and date the colored consent form (pg. 2)
   (Both parent and child must sign if the child is under 18)
3. Complete the colored paper surveys (Parents should help children under age 18)
4. Mail back the colored paper consent form and completed surveys in the addressed envelope (included)
5. Keep the white copy of the consent form for your records

To ensure that you are included in the study, please mail back the signed consent form and completed surveys within two weeks. Please be sure to complete both sides of the surveys. We appreciate your participation and look forward to your response.

Thank you,

Juliann McConnell, M.S., C.G.C.
Genetic Counselor
University of Pittsburgh Medical Center
Children's Hospital of Pittsburgh

Sunecta Madan-Khetarpal, MD
Associate Professor of Pediatrics
University of Pittsburgh Medical Center
Children's Hospital of Pittsburgh

APPENDIX C

CONSENT FORMS

Children's Hospital of Pittsburgh of UPMC

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Name: **Pain and quality of life in connective tissue disorder patients**

Principal Investigator: Suneeta Madan-Khetarpal, MD
Children's Hospital of Pittsburgh
Division of Medical Genetics
4401 Penn Ave
Pittsburgh, PA
Phone: 412-692-5070
Fax: 412-692-6472

Study Coordinator: Tracy Dawson, BS

Co-Investigator: Juliann McConnell, MS, CGC
412-692-5969

Why is this study being done?
We are interested in learning how chronic pain affects the quality of life of children and adults with connective tissue disorders (CTD). We are specifically interested in children and adults with a diagnosis of Ehlers-Danlos syndrome (EDS) and those with mixed CTD. We would like to determine if any pain management techniques help to relieve or reduce pain.

Who is being asked to participate in this study?
We will ask about 100 people with a diagnosis of EDS or mixed connective tissue disorder to complete surveys relating to pain, quality of life, and pain management. Participants must be between the ages of 8 and 80 and diagnosed with EDS OR mixed connective tissue disorder.

What are the possible risks of participating in this study?
There is little risk involved in this study. No invasive procedures or medications are included. The major potential risk is a breach of confidentiality. We will do everything that we can to keep your information confidential and private. To reduce the likelihood of a breach of confidentiality, all surveys will have a unique number. Another potential risk is psychological stress due to the questions on the survey. The questions ask about pain and how that pain affects daily life. This could cause some participants to become more aware of their pain or how the pain affects their life.

Will this study involve the disclosure of my identifiable medical record information?
As part of this study, we are also requesting your authorization or permission to review your medical records to obtain age, diagnosis, and clinical symptoms. We will use this information for data analysis in the study to determine if there are any differences in quality of life based on these factors. You can withdraw your authorization at any time by contacting the research team with a written request.

What does this study involve?
You should complete the enclosed surveys. The surveys will take approximately 15 to 20 minutes to complete. This signed consent form and the completed surveys should be sent back in the enclosed envelope.

Will there be a benefit from being a part of this study?
There are no costs or compensation for participation in the study. There are no direct benefits to you for being involved in the study. We hope to learn more about how chronic pain associated with connective tissue disorders and participation will benefit the knowledge about this topic.

Will anyone know that I participated in this study?
All records relating to your participation in this study are kept strictly confidential and private. All surveys will have a unique number. Your identity will not be revealed in any description of this research. Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable research information for the purpose of monitoring the appropriate conduct of this research study. In unusual cases, the investigators may be required to release identifiable information related to your participation in this research study in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies

Is my participation voluntary?
Participation in this study is completely voluntary. You may refuse to take part in it. You may stop participating at any time even after signing this form. Your decision will not affect your medical care at the Children's Hospital of Pittsburgh in any way.

How can I get more information about this study?
If you would like additional information about this study, you may contact the study coordinator or investigators listed on the first page of this document. Any questions about your rights as a research participant can be answered by the Human Subject Protection Advocate at the University of Pittsburgh IRB Office: 866-212-2668.

I have read the consent form and I agree to participate in the study. I understand that I am encouraged to ask questions about this study to the researchers listed on the first page. I understand that my participation in this study is voluntary and that I am free to refuse to participate or discontinue my participation in this study at any time without affecting my care at this institution. By signing this form I consent to participate in this research study and provide my authorization to share my medical records with the research team.

_____ _____
Subject's Signature Date

VERIFICATION OF EXPLANATION

I certify that I have carefully explained the purpose and nature of this research to the participant. They have had an opportunity to discuss it with me in detail. I have answered all of his/her questions and they freely agreed to participate in this research.

_____ _____
Printed Name of Person Obtaining Consent Role in Research Study

_____ _____
Signature of Person Obtaining Consent Date

Children's Hospital of Pittsburgh of UPMC

PARENTAL CONSENT FOR CHILD TO PARTICIPATE IN A RESEARCH STUDY

Study Name: **Pain and quality of life in connective tissue disorder patients**

Principal Investigator: Suneeta Madan-Khetarpal, MD
Children's Hospital of Pittsburgh
Division of Medical Genetics
4401 Penn Ave Pittsburgh, PA
Phone: 412-692-5070
Fax: 412-692-6472

Study Coordinator: Tracy Dawson, BS

Co-Investigator: Juliann McConnell, MS, CGC
412-692-5969

Why is this study being done?
We are interested in learning how chronic pain affects the quality of life of children and adults with connective tissue disorders (CTD). We are specifically interested in children and adults with a diagnosis of Ehlers-Danlos Syndrome (EDS) and those with mixed CTD. We would like to determine if any pain management techniques help to relieve or reduce pain.

Who is being asked to participate in this study?
We are asking people with a diagnosis of EDS or mixed CTD to complete surveys relating to pain, quality of life, and pain management. Participants must be between the ages of 8 and 80 and diagnosed with EDS OR mixed CTD.

What are the possible risks of participating in this study?
There is little risk involved in this study. No invasive procedures or medications are included. The major potential risk is a breach of confidentiality. We will do everything that we can to keep your child's information confidential and private. To reduce the likelihood of a breach of confidentiality, all surveys will have a unique number. Another potential risk is psychological stress due to the questions on the survey. The questions ask about pain and how that pain affects daily life. This could cause some participants to have become more aware of their pain or how the pain affects their life.

Will this study involve the disclosure of my child's identifiable medical record information?
As part of this study, we are requesting your authorization or permission to review your child's medical records to obtain their age, diagnosis, and clinical symptoms. We will use this information in our data analysis of the study to determine if there are any differences in quality of life based on these factors. You can withdraw your authorization at any time by contacting the research team with a written request.

What does this study involve?
Your child should complete the enclosed surveys with your assistance. The surveys will take approximately 15 to 20 minutes to complete. This signed consent form and the completed surveys should be sent back in the enclosed envelope.

Will there be a benefit from being a part of this study?
There are no costs or compensation for participation in the study. There are no direct benefits to you or your child for being involved in the study. We hope to learn more about how chronic pain associated with CTD and participation will benefit the knowledge about this topic.

Will anyone know that my child has participated in this study?
All records relating to your child's participation in this study are kept strictly confidential and private. All surveys will have a unique number. The identity of your child will not be revealed in any description of this research. Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable

research information for the purpose of monitoring the appropriate conduct of this research study. In unusual cases, the investigators may be required to release identifiable information related to your participation in this research study in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.

Is my participation voluntary?
Participation in this study is completely voluntary. You and/or your child can refuse to take part in it or stop participating at any time, even after signing this form. Your decision will not affect your child's medical care at the Children's Hospital of Pittsburgh.

How can I get more information about this study?
If you or your child would like additional information about this study, you may contact the study coordinator or investigators listed at the beginning of this document. Any questions about your child's rights as a research participant can be answered by the Human Subject Protection Advocate at the University of Pittsburgh IRB Office: 866-212-2668.

.....

_____
Printed Name of Child

I understand that, as a minor (age less than 18 years), the above named child is not permitted to participate in this research study without my consent. Therefore, by signing this form, I give my consent for his/her participation in this research study. By signing this form, I also agree to explain this research study to my child in age-appropriate language and to assist in completing the surveys. I have read the consent form and I agree to participate in the study. I understand that I am encouraged to ask questions about this study to the researchers listed on the first page. I understand that my participation in this study is voluntary and that I am free to refuse to participate or discontinue my participation in this study at any time without affecting my care at this institution. I provide my authorization to share my child's medical records with the research team.

_____ _____
Parent's Signature Date

_____
Relationship to child

FOR CHILDREN

The research has been explained to me, and I agree to participate.

_____ _____
Participant's Signature Date

VERIFICATION OF EXPLANATION

I certify that I have carefully explained the purpose and nature of this research to both the child and parent in age-appropriate language. They have had an opportunity to discuss it with me in detail. I have answered all of his/her questions and they freely agreed to participate in this research.

_____ _____
Printed Name of Person Obtaining Consent Role in Research Study

_____ _____
Signature of Person Obtaining Consent Date

APPENDIX D

SURVEYS

Pain Management Questionnaire

If you are under 18 years old, please have a parent help you to answer these questions.

Have you ever used any of the following to help relieve or reduce pain? Please circle as many as apply.

1. Physical therapy
2. Exercise
3. Pain Medication
4. None
5. Other:_____

What has helped to best relieve or reduce your pain? Please circle only one.

1. Physical therapy
2. Exercise
3. Pain Medication
4. None
5. Other:_____

PAIN QUALITY ASSESSMENT SCALE© (PQAS©)

Instructions: There are different aspects and types of pain that patients experience and that we are interested in measuring. Pain can feel sharp, hot, cold, dull, and achy. Some pains may feel like they are very superficial (at skin-level), or they may feel like they are from deep inside your body. Pain can also be described as unpleasant.

The Pain Quality Assessment Scale helps us measure these and other different aspects of your pain. For one patient, a pain might feel extremely hot and burning, but not at all dull, while another patient may not experience any burning pain, but feel like their pain is very dull and achy. Therefore, we expect you to rate very high on some of the scales below and very low on others.

Please use the 19 rating scales below to rate how much of each different pain quality and type you may or may not have felt ***OVER THE PAST WEEK, ON AVERAGE***.

Place an "X" through the number that best describes your pain. For example:

0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | ~~10~~

1. Please use the scale below to tell us how **intense** your pain has been over the past week, on average.

No pain — 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 — The most **intense** pain sensation imaginable

2. Please use the scale below to tell us how **sharp** your pain has felt over the past week. Words used to describe sharp feelings include "like a knife", "like a spike", or "piercing".

Not sharp — 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 — The most **sharp** sensation imaginable ("like a knife")

3. Please use the scale below to tell us how **hot** your pain has felt over the past week. Words used to describe very hot pain include "burning" and "on fire".

Not hot — 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 — The most **hot** sensation imaginable ("burning")

4. Please use the scale below to tell us how **dull** your pain has felt over the past week.

Not dull — 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 — The most **dull** sensation imaginable

5. Please use the scale below to tell us how **cold** your pain has felt over the past week. Words used to describe very cold pain include "like ice" and "freezing".

Not cold — 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 — The most **cold** sensation imaginable ("freezing")

6. Please use the scale below to tell us how **sensitive** your skin has been to light touch or clothing rubbing against it over the past week. Words used to describe sensitive skin include "like sunburned skin" and "raw skin".

Not sensitive | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **sensitive** sensation imaginable ("raw skin")

7. Please use the scale below to tell us how **tender** your pain is when something has pressed against it over the past week. Another word used to describe tender pain is "like a bruise".

Not tender | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **tender** sensation imaginable ("like a bruise")

8. Please use the scale below to tell us how **itchy** your pain has felt over the past week. Words used to describe itchy pain include "like poison ivy" and "like a mosquito bite".

Not itchy | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **itchy** sensation imaginable ("like poison ivy")

9. Please use the scale below to tell us how much your pain has felt like it has been **shooting** over the past week. Another word used to describe shooting pain is "zapping".

Not shooting | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **shooting** sensation imaginable ("zapping")

10. Please use the scale below to tell us how **numb** your pain has felt over the past week. A phrase that can be used to describe numb pain is "like it is asleep".

Not numb | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **numb** sensation imaginable ("asleep")

11. Please use the scale below to tell us how much your pain sensations have felt **electrical** over the past week. Words used to describe electrical pain include "shocks", "lightning", and "sparking".

Not electrical | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **electrical** sensation imaginable ("shocks")

12. Please use the scale below to tell us how **tingling** your pain has felt over the past week. Words used to describe tingling pain include "like pins and needles" and "prickling".

Not tingling | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **tingling** sensation imaginable ("pins and needles")

13. Please use the scale below to tell us how **cramping** your pain has felt over the past week. Words used to describe cramping pain include "squeezing" and "tight".

Not cramping | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **cramping** sensation imaginable ("squeezing")

14. Please use the scale below to tell us how **radiating** your pain has felt over the past week. Another word used to describe radiating pain is "spreading".

Not radiating | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **radiating** sensation imaginable ("spreading")

15. Please use the scale below to tell us how **throbbing** your pain has felt over the past week. Another word used to describe throbbing pain is "pounding".

Not throbbing | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **throbbing** sensation imaginable ("pounding")

16. Please use the scale below to tell us how **aching** your pain has felt over the past week. Another word used to describe aching pain is "like a toothache".

Not aching | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **aching** sensation imaginable ("like a toothache")

17. Please use the scale below to tell us how **heavy** your pain has felt over the past week. Other words used to describe heavy pain are "pressure" and "weighted down".

Not heavy | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **heavy** sensation imaginable ("weighted down")

18. Now that you have told us the different types of pain sensations you have felt, we want you to tell us overall how **unpleasant** your pain has been to you over the past week. Words used to describe very unpleasant pain include "annoying," "bothersome," "miserable," and "intolerable". Remember, pain can have a low intensity but still feel extremely unpleasant, and some kinds of pain can have a high intensity but be very tolerable. With this scale, please tell us how **unpleasant** your pain feels.

Not unpleasant | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **unpleasant** sensation imaginable ("intolerable")

19. Finally, we want you to give us an estimate of the severity of your deep versus surface pain over the past week. We want you to rate each location of pain separately. We realize that it can be difficult to make these estimates, and most likely it will be a "best guess," but please give us your best estimate.

HOW INTENSE IS YOUR *DEEP* PAIN?

No **deep** pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **intense deep** pain sensation imaginable

HOW INTENSE IS YOUR *SURFACE* PAIN?

No **surface** pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **intense surface** pain sensation imaginable

20. Pain can also have different time qualities. For some people, the pain comes and goes and so they have some moments that are completely without pain; in other words the pain "comes and goes". This is called **intermittent** pain. Others are never pain free, but their pain types and pain severity can vary from one moment to the next. This is called **variable** pain. For these people, the increases can be severe, so that they feel they have moments of very intense pain ("breakthrough" pain), but at other times they can feel lower levels of pain ("background" pain). Still, they are never pain free. Other people have pain that really does not change that much from one moment to another. This is called **stable** pain. Which of these best describes the time pattern of your pain (please select only one):

    ( ) I have **intermittent** pain (I feel pain sometimes but I am pain-free at other times).
    ( ) I have **variable** pain ("background" pain all the time, but also moments of more pain, or even severe "breakthrough pain or varying types of pain).
    ( ) I have **stable** pain (constant pain that does not change very much from one moment to another, and no pain-free periods).

PedsQL™

Pediatric Pain Questionnaire™

Teen Form (13-18 years of age)

Name: _____

Date: _____ **Record Number:** _____

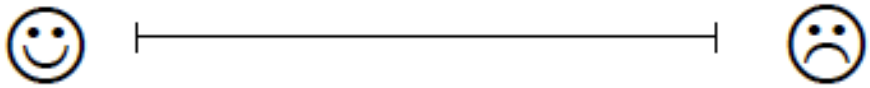
What words would you use to describe your pain or hurt?

_____

_____

_____

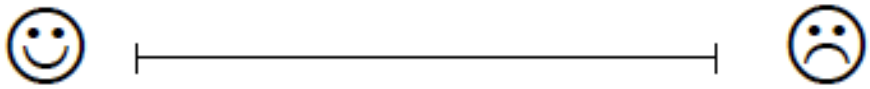
1. Put a mark on the line that best shows **how you feel now.** If you have no pain or hurt, you would put a mark at the end of the line by the happy face. If you have some pain or hurt, you would put a mark near the middle of the line. If you have a whole lot of pain or hurt, you would put a mark by the sad face.



Not hurting
No discomfort
No pain

Hurting a whole lot
Very uncomfortable
Severe Pain

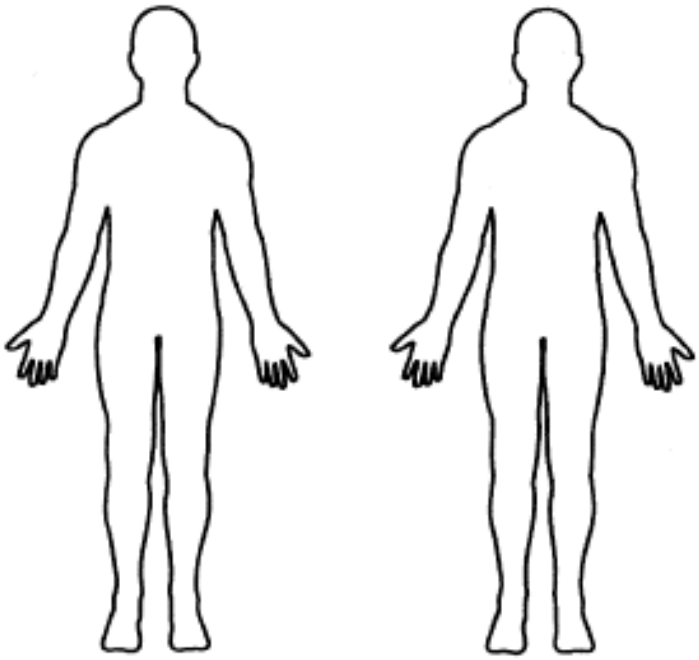
2. Put a mark on the line that best shows what was the **worst pain you had this week.** If you had no pain or hurt this week, you would put a mark at the end of the line by the happy face. If you had some pain or hurt, you would put a mark by the middle of the line. If the worse pain you had was a whole lot of pain, you would put a mark by the sad face.



Not hurting
No discomfort
No pain

Hurting a whole lot
Very uncomfortable
Severe Pain

Please mark an **X** on the **exact** place where you are having pain now. If there is more than one painful place, mark them '1', '2', '3', etc., starting with the most painful place as '1'.



PedsQL™

Pediatric Pain Questionnaire™

Child Form (8-12 years of age)

Name: _____

Date: _____ **Record Number:** _____

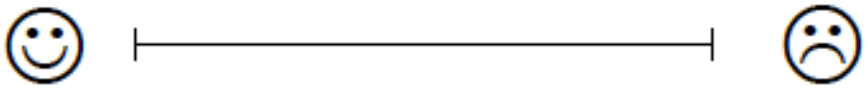
What words would you use to describe your pain or hurt?

_____

_____

_____

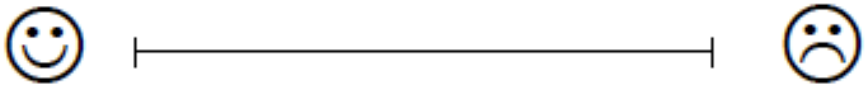
1. Put a mark on the line that best shows **how you feel now**. If you have no pain or hurt, you would put a mark at the end of the line by the happy face. If you have some pain or hurt, you would put a mark near the middle of the line. If you have a whole lot of pain or hurt, you would put a mark by the sad face.



Not hurting
No discomfort
No pain

Hurting a whole lot
Very uncomfortable
Severe Pain

2. Put a mark on the line that best shows what was the **worst pain you had this week**. If you had no pain or hurt this week, you would put a mark at the end of the line by the happy face. If you had some pain or hurt, you would put a mark by the middle of the line. If the worse pain you had was a whole lot of pain, you would put a mark by the sad face.

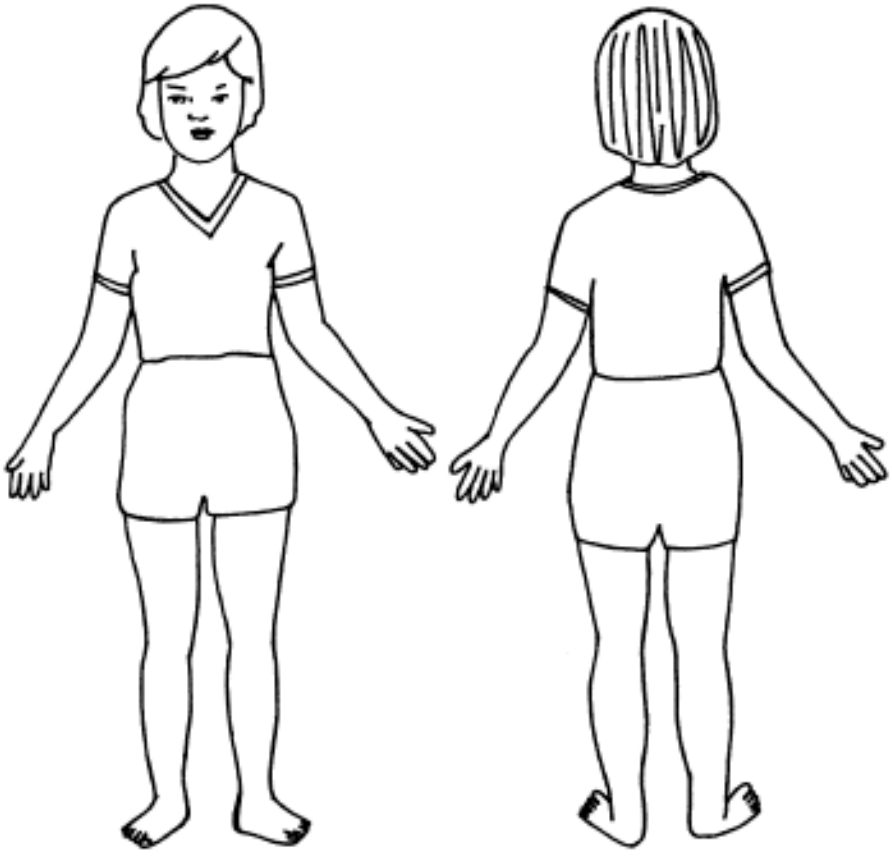


Not hurting
No discomfort
No pain

Hurting a whole lot
Very uncomfortable
Severe Pain

Pick the colors that mean **No hurt, A little hurt, More hurt,** and **A lot of hurt** to you and color in the boxes. Now, using these colors, color in the body to show how you feel. Where you have no hurt, use the **No hurt** color to color in your body. If you have hurt or pain, use the color that tells how much hurt you have.

No pain No hurt	Mild pain A little hurt	Moderate pain More hurt	Severe pain A lot of hurt



Front Back

ID# _____

Date: _____

PedsQL™

Adult Quality of Life Inventory

Version 4.0

ADULT REPORT

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

In the past ONE month, how much of a problem has this been for you …

ABOUT MY HEALTH AND ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other adults	0	1	2	3	4
2. Other adults do not want to be my friend	0	1	2	3	4
3. Other adults tease me	0	1	2	3	4
4. I cannot do things that others my age can do	0	1	2	3	4
5. It is hard to keep up with my peers	0	1	2	3	4

ABOUT MY WORK/STUDIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention at work or school	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my work or studies	0	1	2	3	4
4. I miss work or school because of not feeling well	0	1	2	3	4
5. I miss work or school to go to the doctor or hospital	0	1	2	3	4

ID# _____

Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

TEEN REPORT (ages 13-18)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

In the past ONE month, how much of a problem has this been for you …

ABOUT MY HEALTH AND ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other teens	0	1	2	3	4
2. Other teens do not want to be my friend	0	1	2	3	4
3. Other teens tease me	0	1	2	3	4
4. I cannot do things that other teens my age can do	0	1	2	3	4
5. It is hard to keep up with my peers	0	1	2	3	4

ABOUT SCHOOL *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

ID# _____

Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

CHILD REPORT (ages 8-12)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

In the past ONE month, how much of a problem has this been for you …

ABOUT MY HEALTH AND ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other kids	0	1	2	3	4
2. Other kids do not want to be my friend	0	1	2	3	4
3. Other kids tease me	0	1	2	3	4
4. I cannot do things that other kids my age can do	0	1	2	3	4
5. It is hard to keep up when I play with other kids	0	1	2	3	4

ABOUT SCHOOL *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

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